Journal Club:

Change in brain network connectivity during PACAP38-induced migraine attacks

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There is evidence to suggest that migraine attacks involve changes in complex neuronal networks that can be measured using functional MRI (fMRI) methods including resting state functional connectivity (RSFC). Networks that have previously been shown to be involved in the sensory and affective aspects of pain perception include the default mode network (DMN), salience network (SN), and sensorimotor network (SMN) (figure).¹ In a recent study, Amin et al.² examined the RSFC of these 3 networks at baseline and in the early phases of experimentally induced migraine in patients with migraine without aura. In order to capture the early phases of migraine, corresponding to the time closest to migraine attack onset, migraine attacks were induced using the potent vasodilator neuropeptide pituitary adenylate cyclase-activating polypeptide-38 (PACAP38).³ Since vasodilators can alter hemodynamics and potentially confound the fMRI signal, another vasodilator, vasoactive intestinal peptide (VIP), was used as a control since it also acts on extracranial arteries, but is much less likely (<20%) to provoke migraine-like attacks.³

HYPOTHESIS AND DESIGN Amin et al. hypothesized that patients would have altered RSFC of the DMN, SN, and SMN during the early phases of migraine compared to baseline. Abnormalities in the connectivity and activity of these resting-state networks have previously been reported during the interictal phase of migraine.^{4,5}

Patients were recruited as part of a larger study investigating the migraine-inducing properties of PACAP38 and VIP and their effects on extracranial and intracranial arterial diameter among other factors.³ A double-blind randomized design was used to allocate 24 patients to receive an IV infusion of either PACAP38 (10 pmol/kg/min) or VIP (8 pmol/kg/min) over 20 minutes on the first study day. On the second study day, which occurred at least 1 week after the first, patients received an infusion of the alternate vasodilator (i.e., the one they did not receive on the first day). Resting-state fMRI scans were acquired at baseline and at fixed timepoints thereafter.

METHODS Eligible female participants meeting the inclusion criteria were included in the study if they had a verified diagnosis of migraine without aura according to the International Classification of Headache Disorders II. Resting-state fMRI scans were acquired at baseline and at 3 fixed time points after the start of infusion: 30, 130, and 310 minutes. An exception was if patients reported a migraine-like attack, in which case they were scanned immediately. Patients were migraine-free for 5 days and headache-free for 48 hours prior to baseline scans. To examine the early phase of PACAP38-induced migraine, the preattack time point that was closest to the attack onset was used in the RSFC analyses. The PACAP38 group consisted of 16 patients who all experienced migraine attacks after PACAP38 infusion, and the VIP group comprised 15 patients, none of whom reported migraine attacks after VIP infusion. Functional connectivity of the SN, DMN, and SMN were examined. Voxels within each of these networks were averaged and submitted to a correlation analysis with the rest of the voxels in the brain. The resulting correlation maps of the predrug and postdrug sessions were compared using a paired *t* test.

RESULTS The authors report significant ($p < 0.05$, familywise error corrected) connectivity changes in each of the resting-state networks examined in the early phase of migraine compared to baseline for the PACAP38 group only. Specifically, following PACAP38 infusion, there was increased connectivity between the SN and the inferior frontal gyri bilaterally, increased connectivity between the SMN and the right premotor cortex, decreased connectivity between the SMN and the left visual cortex, and increased connectivity between DMN and the right cerebellum and left frontal lobe.

INTERPRETATION In their study, Amin et al. demonstrated altered RSFC patterns in the DMN, SN, and SMN in the early phases of PACAP38-induced migraine attacks. In the Discussion, the authors propose that the observed connectivity alterations

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Left panel: the default mode network includes the precuneus/posterior cingulate cortex, anterior cingulate cortex, and the temporoparietal junction; middle panel: the salience network encompasses the frontoinsula and anterior cingulate cortices; right panel: the sensorimotor network includes the supplementary motor area/midcingulate cortex, bilateral primary motor cortex, and bilateral middle frontal gyri. This figure was adapted from Heine et al.¹ (Copyright: Heine, Soddu, Gomez, et al., distributed under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in other forums, provided the original authors are credited.)

may reflect pain, cognitive, or emotional changes associated with experiencing a migraine attack.

There were several strengths to this study. To ensure that PACAP38-induced changes in RSFC were not merely a reflection of changes in vasodilation, the authors included a VIP control group and used a double-blind randomized design to assess patients under both conditions.

Another strength was the use of familywise error corrections to control for multiple comparisons. These corrections control for the probability of obtaining type I (false-positive) errors. This approach helps to ensure that alterations in connectivity following PACAP38 infusion were attributable to the experimental manipulation and not merely due to chance.

This study also helped provide insight into whether altered connectivity predisposes individuals to migraine (brain state), or whether connectivity alterations are induced by migraine attacks over time (brain trait). Previous fMRI studies examining migraineurs during the interictal phase have reported RSFC abnormalities. However, the paucity of longitudinal data has precluded the inference of a causal relationship.⁶ Since the current study describes intra-individual changes in connectivity from baseline to

early-phase migraine, it arguably supports the brain trait model of connectivity abnormalities, in agreement with a previous study that reported progressive abnormalities in connectivity over 6 weeks in patients with worsening migraines.⁷

Some limitations to the study include the following:

1. Lack of cognitive or psychiatric tests. In their Discussion, the authors suggest that the resting-state alterations observed following PACAP38 administration may reflect pain, cognitive, or emotional changes associated with experiencing a migraine attack. By including objective psychometric testing, it may be possible to determine some of the behavioral correlates of the RSFC changes.
2. Broad definition of early phase migraine. A significant proportion of patients who developed PACAP38-induced migraine were asymptomatic and pain-free at the time of their postinfusion scan, while the remainder had mild/moderate pain and other migrainous features. This introduces heterogeneity into the compared imaging, as the presence of pain is a highly salient stimulus that may be expected to alter resting state network connectivity. In addition, prodromal features were

not described. Therefore, it is unclear if some of the RSFC alterations could be explained by these symptoms.

3. Lack of a healthy control group. While patients with migraine served as their own controls in the PACAP38 and VIP conditions, the inclusion of healthy controls could help determine if observed RSFC alterations are specific to migraine patients, or if they reflect induced migraines in general.
4. Patient selection and generalizability. Only female patients without aura and certain comorbidities were included in the study. It can be challenging to balance recruiting a homogeneous sample and one that is representative of the larger population. Future studies may overcome this selection issue by recruiting a larger sample more representative of patients and accounting for variables such as sex in the statistical analyses (e.g., analysis of covariance or multiple linear regression model approaches).
5. Lack of migraine history. Migraine frequency and duration data were not included; therefore the impact of these variables on RSFC alterations could not be assessed. It was also unclear if any patients received a diagnosis of chronic migraine.
6. Vasodilation as a potential confounding factor in the interpretation of the blood oxygen level-dependent (BOLD) signal. fMRI captures changes in the BOLD signal, which reflects the ratio of oxygenated and deoxygenated hemoglobin. Alterations in hemodynamics have the potential to confound interpretations associated with BOLD signal changes. VIP and PACAP38 are both potent vasodilators but are not identical in their vasodilatory properties. PACAP38 induces dilation of extracranial arteries and is markedly abnormal at 120 minutes postinfusion, while the dilation induced by VIP is fully resolved.³ This difference may be significant to the interpretation of this study's findings, as the median time for the scan in the early phases of migraine was at 130 minutes postinfusion. Additionally, heart rate was significantly higher and blood pressure significantly lower after PACAP38 infusion compared to VIP² and these physiologic differences may confound the resting-state results if not regressed out.
7. Interpretation of the SMN network connectivity with visual cortex as representing photophobia. While it has been previously established that loss of functionality in this region may be associated with diminished activity of a visuotrigeminal pathway resulting in headache and photophobia,⁸ only 6 patients out of 16 in the PACAP38-induced

migraine group reported photophobia at the time of the scan. Future studies comparing visual cortex connectivity at baseline and after the onset of photophobia are warranted.

This study provides insight into RSFC alterations that occur during the early phases of migraine. PACAP38-induced migraines are unlikely to differ functionally from spontaneous migraines in migraineurs since patients cannot differentiate them and they respond well to triptan therapies, which effectively treat migraine pain when taken early.^{2,3} The mechanisms by which PACAP38 induces migraine are not completely understood, but are unlikely to be explained solely by prolonged vasodilation. Other possible mechanisms include sensitization of perivascular trigeminal afferents by vasoactive and neurogenic inflammatory pathways, mast cell degranulation, calcitonin gene-related peptide release from the trigeminal nucleus caudalis, and systemic effects.^{3,9} Further comparison studies of PACAP38-induced migraine and spontaneous migraine are required to validate this model, which has exciting therapeutic implications in the form of pituitary adenylate cyclase-activating polypeptide type I receptor antagonists.

AUTHOR CONTRIBUTIONS

Dr. DeSouza: concept and design for manuscript content, interpretation of findings, critical revision of the manuscript for important intellectual content. Dr. O'Hare: concept and design for manuscript content, interpretation of findings, critical revision of the manuscript for important intellectual content. Dr. Woldeamanuel: concept and design for manuscript content, interpretation of findings, critical revision of the manuscript for important intellectual content. Dr. Cowan: critical revision of the manuscript for important intellectual content, study supervision.

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