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Brainstem functional oscillations across the migraine cycle: A longitudinal investigation

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ABSTRACT

Although the mechanisms responsible for migraine initiation remain unknown, recent evidence shows that brain function is different immediately preceding a migraine. This is consistent with the idea that altered brain function, particularly in brainstem sites, may either trigger a migraine or facilitate a peripheral trigger that activates the brain, resulting in pain. The aim of this longitudinal study is therefore to expand on the above findings, and to determine if brainstem function oscillates over a migraine cycle in individual subjects. We performed resting state functional magnetic resonance imaging in three migraineurs and five controls each weekday for four weeks. We found that although resting activity variability was similar in controls and interictal migraineurs, brainstem variability increased dramatically during the 24-hour period preceding a migraine. This increase occurred in brainstem areas in which orofacial afferents terminate: the spinal trigeminal nucleus and dorsal pons. These increases were characterized by increased power at infra-slow frequencies, principally between 0.03 and 0.06 Hz. Furthermore, these power increases were associated with increased regional homogeneity, a measure of local signal coherence. The results show within-individual alterations in brain activity immediately preceding migraine onset and support the hypothesis that altered regional brainstem function before a migraine attack is involved in underlying migraine neurobiology.

1. Introduction

The pathophysiology of migraine has been hotly debated for years as either originating from vascular and/or centrally-driven mechanisms. The most prevalent hypothesis for the initiation of a migraine attack centres around the idea that sensitization of meningeal nociceptors leads to activation of trigeminovascular neurons that enter the central nervous system and evoke debilitating head pain (Bernstein and Burstein, 2012; Borsook and Burstein, 2012). More recently, an alternative idea of a "central generator" has been proposed, which posits that changes within the central nervous system initiate migraine attacks, even though the idea that a peripheral cerebrovascular trigger is not necessary for migraine initiation has been vigorously debated (Borsook and Burstein, 2012). Indeed, it has been suggested that cerebrovascular inputs may only trigger a migraine if the brain, in particular brainstem regions involved in mediating head pain, are in a sensitive state (Burstein et al., 2015). That is, the brainstem oscillates between a state where incoming cerebrovascular inputs can evoke head pain to a state where the same inputs are prevented from travelling to the cortex and evoking head pain.

Consistent with this brainstem oscillation theory, we recently explored the notion of cyclic changes throughout the migraine cycle in a series of cross-sectional studies. We found that during the 24-hour period immediately before a migraine attack, brain regions that process orofacial noxious information such as the spinal trigeminal nucleus (SpV), midbrain periaqueductal gray matter (PAG), dorsal pons and hypothalamus display increases in resting signal variations in the infra-slow frequency range (Meylakh et al., 2018). Furthermore, during this 24-hour period there is an increased coupling strength between activity in the PAG and the hypothalamus. Interestingly, these same brainstem regions have been shown to be activated during a migraine itself (Afridi et al., 2005a; Bahra et al., 2001; Denuelle et al., 2007; Matharu et al.,

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2004), raising the prospect that the changes in activity within the trigeminal pain pathway immediately prior to a migraine are precursors to subsequent activity increases and the development of migraine head pain.

Whilst we have shown resting brainstem activity pattern changes immediately prior to a migraine in cross-sectional studies, it remains unknown if these changes also occur in individuals over a full migraine cycle. It is possible that changes in resting activity patterns occur on a daily basis, being more variable in migraineurs and trigger a migraine attack only when coupled to an appropriate external trigger. Though there are obvious logistical difficulties in exploring brain function in an individual subject over weeks, given the individual variability in migraine attack occurrence, direct evidence of within-person alterations prior to migraine onset would strengthen the evidence of a precursor state. Indeed, recent longitudinal fMRI studies over the migraine cycle have shown activation of the hypothalamus as a result of painful trigeminal stimulation within the 48 h preceding a migraine headache (Schulte et al., 2020a), as well as increased functional connectivity between the nucleus accumbens and the dorsal rostral pons within the 24 h preceding a migraine headache (Schulte et al., 2020b). The aim of this longitudinal investigation is therefore to expand on the above findings, and to determine if brainstem function oscillates over a migraine cycle in individual subjects. We hypothesise that, consistent with our cross-sectional results, the pattern of resting signal intensity characterized by increased resting activity variability and infra-slow oscillations will occur in the ascending trigeminal pathway immediately prior to a migraine attack.

2. Methods

2.1. Subjects

Three subjects with migraine (2 females, ages 21 and 26; 1 male, age 25) and five pain-free controls (3 females, 2 males; mean age 30.4 ± 4.2 years [±SEM]) were recruited for the study from the general population using an advertisement. There were no statistically significant differences in age (*t*-test, $p > 0.05$) or sex (chi-squared test, $p > 0.05$) between the two subject groups. Migraine subjects were diagnosed according to the IHS Classification ICHD-3 BETA criteria and none of the migraine subjects reported an aura associated with their migraine attacks. Migraine subject characteristics, including medication use are shown in Table 1.

All three migraineurs had episodic migraine. We attempted to scan each migraineur daily, from Monday to Friday over four weeks. Two migraineurs completed all 20 scanning sessions and one migraineur completed 19 scanning sessions. All three migraineurs were scanned during three migraine periods: (i) interictal, at least 72 h after and 24 h prior to a migraine attack; (ii) immediately (within 24 h) prior to an attack; (iii) immediately (within 72 h) following an attack. Subjects did not report experiencing any prodromal symptoms during the 24-hour period prior to an attack. Migraine subject 1 (M1) was scanned a total of 20 times; 15 interictal periods, 2 immediately prior to a migraine (2 and 20 h before start of a migraine) and 2 immediately following a migraine (20 and 48 h following the end of a migraine). The last session was excluded due to image acquisition issues. Migraine subject 2 (M2) was scanned 20 times; 12 interictal periods, 2 immediately prior to a migraine (1 h and 5 h before start of a migraine) and 4 immediately following a migraine (12 and 36 h following the end of each migraine). The last session was also excluded due to image acquisition issues. Migraine subject 3 (M3) was scanned 19 times; 16 interictal periods, 1 immediately prior to a migraine (14 h before start of a migraine) and 1 immediately following a migraine (53 h following end of a migraine). One session was excluded due to image acquisition difficulties.

Exclusion criteria for controls were the presence of any pain condition including family history of migraines, current use of analgesics, or any neurological disorder. Exclusion criteria for migraineurs were any other pain condition or neurological disorder. No migraineur was excluded based on their medication use and no migraine or control subject had an incidental neurological finding. All migraineurs indicated the intensity (6-point visual analogue scale; 0 = no pain, 5 = most intense imaginable pain) and drew the facial distribution of pain commonly experienced during a migraine attack. In addition, each subject described the qualities of their migraines and indicated any current treatments used to prevent or abort a migraine once started. Informed written consent was obtained for all procedures according to the Declaration of Helsinki and the local Institutional Human Research Ethics Committees approved the study.

2.2. MRI acquisition

Subjects lay supine on the bed of a 3 Tesla magnetic resonance imaging (MRI) scanner (Philips, Achieva) with their head immobilized in a 32-channel transmit-receive head coil. Scans were acquired five days a week (Monday-Friday) for four weeks. For the first scan only, with each subject relaxed and at rest, a high-resolution 3D T1-weighted anatomical image set, covering the entire brain, was collected (turbo field echo; field of view = 250x250mm, matrix size = 288x288, slice thickness = 0.87 mm, repetition time = 5600 ms; echo time = 2.5 ms, flip angle = 8°). Following this, during the first scanning session, and on every consecutive scan, a series of 180 gradient echo echo-planar functional MRI image volumes using blood oxygen level dependent (BOLD) contrast were collected. Each image volume contained 35 axial slices covering the entire brain (field of view = 240 × 240 mm, matrix size = 80 × 78, slice thickness = 4 mm, repetition time = 2000 ms; echo time = 30 ms, flip angle = 90°).

2.3. Image preprocessing

Using Statistical Parametric Mapping version 12 (SPM12) (Friston et al., 1995) and custom Matlab software, all functional MRI (fMRI) images were realigned and effects of movement modelled and removed from the resting signal intensity of each voxel. In no subject's scan was there significant movement (>0.5 mm in any direction) and all sessions were used for the subsequent analysis. Images were then processed using the Dynamic Retrospective Filtering algorithm (Särkkä et al., 2012), a Bayesian method for physiological noise correction to reduce the potential effects of physiological noise on results. A cardiac frequency band of 60–120 beats per minute (+1 harmonic) and a respiratory frequency band of 8–25 breaths per minute (+1 harmonic) were removed. Global signal intensity changes were removed using the method described by Macey and colleagues (Macey et al., 2004), and the images were then co-registered to each individual's T1-weighted anatomical image set. Using brainstem-specific isolation software (SUIT toolbox) (Diedrichsen, 2006), a mask of the brainstem was created on the T1-weighted anatomical image set and each of the subject's fMRI image sets. Using these masks, the brainstem of the T1 and each of the fMRI image sets

Table 1
Migraine subject characteristics.

Subject	Age	Sex	Years suffering	Pain Side	Aura	Migraine/month	Intensity (0–5)	Medication taken during migraine	Daily medication
M1	21	Female	1.5	left	no	2	3	Ibuprofen, paracetamol, codeine	oral contraceptive pill
M2	25	Male	12	left	no	2	4	Paracetamol	Ciprimal
M3	26	Female	9	right	no	1	3	Ibuprofen	Levlen ED

were isolated and then spatially normalised to a brainstem-specific template in Montreal Neurological Institute (MNI) space. In all analyses, the anatomical locations of significant clusters were confirmed using the Atlas of the Human Brain (Mai et al., 2007) and the Atlas of the Human Brainstem (Paxinos and Huang, 1995).

2.4. Resting brainstem variability

To assess resting variability of each fMRI scan, a brainstem map of resting signal variation as measured by the standard deviation was created for each daily fMRI scan in each migraineur and control subject. These signal variability maps were smoothed using a 3 mm full-width-half-maximum (FWHM) Gaussian filter and the three migraineurs' image sets were then placed into a voxel-by-voxel fixed effects analysis. Using a boxcar model design where days immediately prior to a migraine were set to "1″ and all other days "0", significant increases and decreases in variability were determined across all three migraineurs ($p < 0.05$, false discovery rate (FDR) corrected, minimum 5 contiguous voxels). For each significant cluster, the variability was extracted for each session in each control and migraineur, the average (±SEM) variability calculated and plotted for controls and migraineurs during the interictal, immediately prior to migraine and immediately following migraine days.

The signal variability of the entire brainstem was also determined and plotted for each session in each control and migraineur subject. In addition, for each significant cluster, power spectra were calculated from the resting state signals, and the interictal period was subtracted from power immediately prior to migraine in all three migraineurs. The resulting plot of power difference revealed, as we have previously shown, areas such as the SpV and dorsal pons displaying greater power in the 0.03–0.06 Hz frequency band during the period immediately prior to a migraine compared with the interictal period. To ensure that any variability difference during the period immediately prior to a migraine was not due to differences in head movement, we measured the variability as standard deviation of each migraine and control subject, and 6 movement parameters were created during the realignment preprocessing step (x, y, z, yaw, roll, tilt). Significant differences between controls and each migraine period (2 sample t-tests, $p < 0.05$) and between migraine periods (paired t-tests, $p < 0.05$) were then determined.

2.5. Resting infra-slow (0.03–0.06 Hz) oscillation power

Using the DPARSFA toolbox, raw infra-slow oscillation (ISO) power between 0.03 and 0.06 Hz was calculated for each brainstem voxel for each session of each migraineur and control subject. The resulting ISO power maps were smoothed using a 3 mm FWHM Gaussian filter and the three migraineurs' image sets were placed into a voxel-by-voxel fixed effects analysis. Using a boxcar model design identical to that described above, significant increases and decreases in power were determined across all three migraineurs ($p < 0.001$, minimum 5 contiguous voxels). For each significant cluster, power values were extracted for each session in each control and migraineur, and the average (±SEM) power was calculated and plotted for controls and migraineurs during the interictal, immediately prior to migraine and immediately following migraine days. In addition, for each significant cluster, power spectra were calculated from the resting state signals during the interictal and immediately prior to migraine periods in all three migraineurs. The power spectra from these clusters were then plotted. In addition, to assess potential laterality, we reflected significant clusters across the midline and extracted ISO power values ipsilateral and contralateral to the migraine headache side.

2.6. Regional homogeneity

To assess local signal covariation, we assessed regional homogeneity, i.e., the similarity of time series within each voxel and its 19 nearest neighbours were measured by calculating Kendall's coefficient of concordance. The resulting brainstem maps were smoothed using a 3 mm FWHM Gaussian filter and the three migraineurs' image sets were placed into a voxel-by-voxel fixed effects analysis. Using a boxcar model design identical to that described above, significant increases and decreases in homogeneity were determined across all three migraineurs ($p < 0.001$, minimum 5 contiguous voxels). For each significant cluster, regional homogeneity values were extracted for each session in each control and migraineur, and the average (±SEM) homogeneity calculated and plotted for controls and migraineurs during the interictal, immediately prior to migraine and immediately following migraine days. The overlap between changes in ISO and regional homogeneity was also determined. Regional homogeneity and ISO values were extracted from each of these clusters in each migraineur and plotted and significant linear relationships determined (Pearson correlation $p < 0.05$).

3. Results

All three migraineurs had at least one migraine attack during the four week scanning period, although none were being scanned at the time of the migraine itself. Analysis of brainstem resting activity variability revealed significantly increased standard deviation of the resting signal specifically during the 24-hour period immediately prior to a migraine in important brainstem pain processing regions (Chudler and Dong, 1995; DaSilva et al., 2002; Fields and Heinricher, 1985; Ossipov et al., 2010) including the left SpV (mean ± SEM variability: controls: 30.6 ± 4.6; interictal: 29.2 ± 7.8; immediately prior to migraine 67.6 ± 48.4; immediately following migraine 32.8 ± 7.3), right SpV (controls: 21.1 ± 1.0; interictal: 20.7 ± 2.3; immediately prior to migraine 46.4 ± 29.3; immediately following migraine 20.2 ± 2.5), PAG (controls: 15.8 ± 1.4; interictal: 15.0 ± 0.9; immediately prior to migraine 24.8 ± 12.1; immediately following migraine 16.6 ± 1.5) and left substantia nigra (SN) (controls: 13.0 ± 1.4; interictal: 8.3 ± 1.8; immediately prior to migraine 15.5 ± 11.4; immediately following migraine 7.8 ± 1.6) as well as one of the key regions implicated in migraine pathophysiology (Afridi et al., 2005a; Denuelle et al., 2007; Meylakh et al., 2018); the left dorsolateral pons (dlPons) (controls: 11.6 ± 0.3; interictal: 13.8 ± 1.6; immediately prior to migraine 23.4 ± 7.2; immediately following migraine 12.8 ± 1.3), and right dlPons (controls: 16.5 ± 0.6; interictal: 16.2 ± 1.5; immediately prior to migraine 31.0 ± 19.2; immediately following migraine 15.9 ± 2.0) (Fig. 1A, Table 2). In no region was variability significantly reduced during the period immediately prior to a migraine.

Plots of individual subjects' total brainstem variability revealed that the day-to-day variability of resting brainstem signal intensity was relatively consistent between controls and migraineurs (Fig. 1B). However, in each migraineur there was a large increase in total brainstem variability on one or two days, which were, as evidenced by the results above, only on those days immediately prior to a migraine. In accordance with our previous cross-sectional studies, plots of the power differences in significantly different clusters between the immediately prior to migraine and interictal periods revealed a consistent increase in power between 0.03 and 0.06 Hz in the left and right SpV and the left and right dlPons (Fig. 1C). These variability differences were not related to head movement since we found no significant difference between the variability of x, y, z, yaw, roll or tilt movement parameters between controls and any migraine period, or between any of the migraine periods (all $p > 0.05$).

A targeted voxel-by-voxel analysis of ISO power (0.03–0.06 Hz) revealed a similar pattern of difference (Fig. 2, Table 2). Increased ISO power occurred in numerous brainstem regions immediately prior to a migraine, including the right SpV (mean ± SEM 0.03–0.06 Hz power: controls: 3.72 ± 0.13; interictal: 3.71 ± 0.13; immediately prior to migraine 5.00 ± 0.81; immediately following migraine 3.89 ± 0.18) left dlPons (controls: 2.82 ± 0.03; interictal: 3.33 ± 0.37; immediately prior

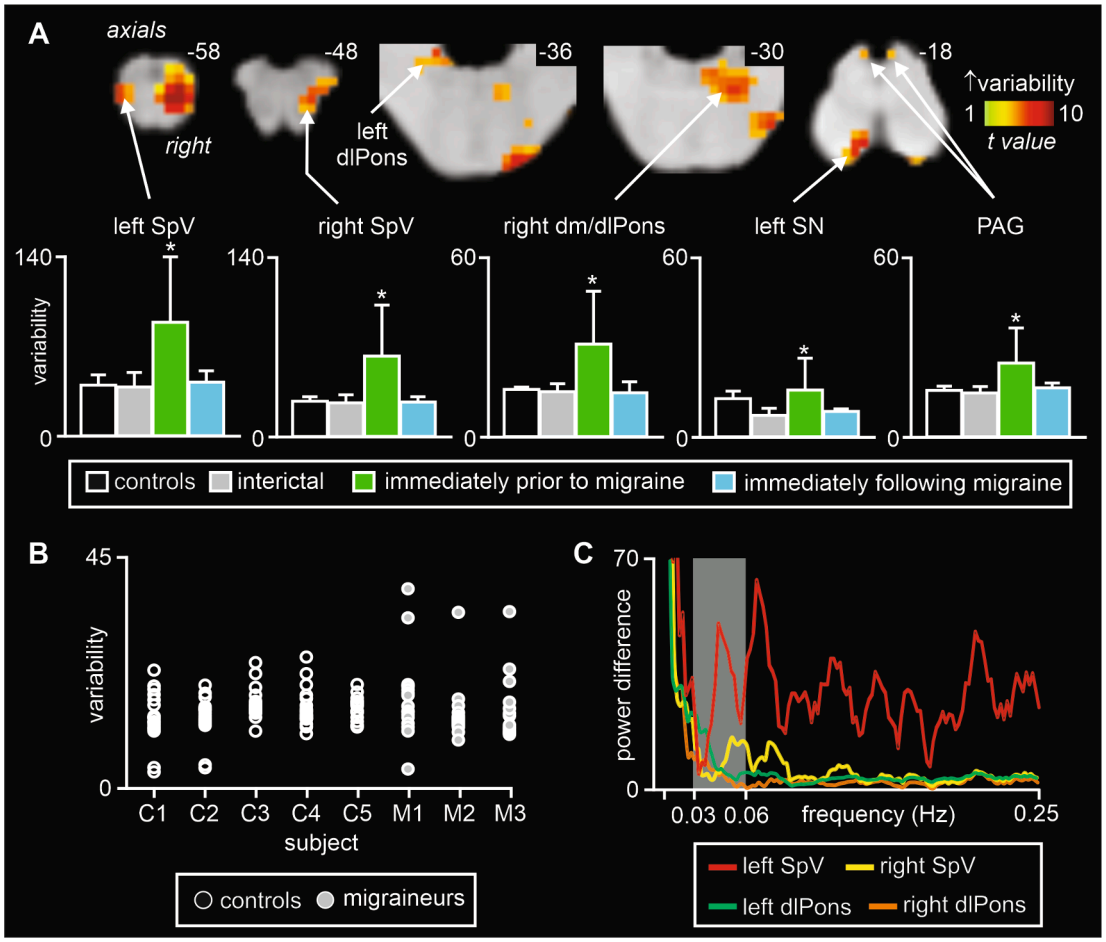

Fig. 1. A: Significant increases (hot colour scale) in resting signal variability in migraineurs during the 24-hour period prior to the onset of a migraine. Increases are overlaid onto axial slices of a T1-weighted anatomical template of the brainstem. Below are plots of mean (±SEM) variability (standard deviation) in controls and migraineurs for the left spinal trigeminal nucleus (SpV), right SpV, right dorsomedial/dorsolateral pons (dm/dlPons), left substantia nigra (SN) and midbrain periaqueductal gray matter (PAG). The slice locations in Montreal Neurological Institute space are indicated at the top right of each slice. B: Plots of total brainstem variability in five controls (C1-5) and three migraine subjects (M1-3) for each scanning session. C: Plots of the power differences between the immediately prior to migraine and interictal periods for the left and right SpV and left and right dlPons. Positive values indicate greater power immediately prior to a migraine compared with the interictal period. The grey shading indicates the frequency band 0.03–0.06 Hz. *p < 0.05 voxel-by-voxel analysis.

to migraine 4.43 ± 0.50; immediately following migraine 3.25 ± 0.33), right dlPons/dorsomedial pons (controls: 2.69 ± 0.04; interictal: 3.19 ± 0.51; immediately prior to migraine 4.15 ± 0.89; immediately following migraine 3.10 ± 0.42) and the left SN (controls: 2.76 ± 0.04; interictal: 2.51 ± 0.06; immediately prior to migraine 3.21 ± 0.64; immediately following migraine 2.41 ± 0.12). The PAG did not display any significant difference at this restricted frequency band. Notably, in no region was ISO power significantly reduced in the period immediately prior to a migraine. Assessment of ISO power with respect to migraine side revealed that in 4 of the 5 immediately prior to migraine scans, ISO power was greater in the ipsilateral compared with contralateral SpV. Similarly, for the dlPons, 4 of the 5 scans were consistently greater on the ipsilateral side for one cluster and contralateral for the other dlPons cluster.

Plots of individual power spectra revealed a consistent power increase in low infra-slow frequencies immediately prior to a migraine compared with the interictal period (Fig. 3). In particular, this power increase occurred at frequencies between 0.03 and 0.06 Hz in the SpV and dlPons in all three migraineurs. In two of the migraineurs (subjects M1 and M3) these power increases appeared to peak at regular frequency intervals; for subject M3 these peaks occurred in the SpV with remarkable regularity at approximately 0.025 Hz apart. In addition, plots of ISO power in each migraineur during the 20 day scanning period revealed that power consistently increased immediately prior to a migraine in the SpV and dlPons (Fig. 4).

Finally, an analysis of regional homogeneity revealed that immediately prior to a migraine, significant increases occurred in most of the same brainstem regions in which there were increases in variability and infra-slow oscillations (Fig. 5). That is, increases occurred in the region of the right SpV (mean ± SEM regional homogeneity: controls: 1.78 ± 0.03; interictal: 1.87 ± 0.10; immediately prior to migraine 2.50 ± 0.41; immediately following migraine 1.91 ± 0.15), right dl/dmPons (controls: 2.64 ± 0.03; interictal: 2.91 ± 0.07; immediately prior to migraine 3.49 ± 0.15; immediately following migraine 2.84 ± 0.03) and the left SN (controls: 2.19 ± 0.09; interictal: 2.32 ± 0.16; immediately prior to migraine 2.71 ± 0.06; immediately following migraine 2.34 ± 0.20). In no region was regional homogeneity significantly reduced in the period immediately prior to a migraine. Finally, we assessed whether there were brainstem areas that displayed increases in both regional homogeneity and ISO and three regions emerged: the right SpV, right dl/dmPons and the left SN. Interestingly, in all three migraineurs, there were significant positive relationships between regional homogeneity and ISO in the right SpV (subject M1: $r = 0.56 p = 0.01$; subject M2: $r = 0.80 p < 0.001$; subject M3: $r = 0.76 p < 0.001$) and right dl/dmPons (subject M1: $r = 0.60 p = 0.006$; subject M2: $r = 0.87 p < 0.001$; subject M3: $r = 0.66 p = 0.003$) but not the left SN (subject M1: $r = -0.07 p = 0.76$; subject M2: $r = -0.17 p = 0.48$; subject M3: $r = 0.10 p = 0.71$).

Table 2
Montreal Neurological Institute (MNI) coordinates, cluster size and t-score for regions of significant increases in resting variability, amplitude of infra-slow oscillations and regional homogeneity immediately prior to a migraine.

Brain region	MNI Co-ordinate			Cluster size	t-score
	x	y	z		
Variability					
Midbrain periaqueductal gray matter	0	−38	−19	12	5.73
Left substantia nigra	−2	−14	−21	83	9.34
Right dorsolateral pons	10	−18	−37	153	8.56
Left dorsolateral pons	−8	−44	−35	17	6.31
Right spinal trigeminal nucleus	4	−40	−61	118	12.22
Left spinal trigeminal nucleus	−6	−40	−61	20	9.99
Infra-slow oscillations (0.03–0.06 Hz)					
Left substantia nigra	−4	−16	−7	14	3.43
Right dorsolateral pons	6	−34	−35	8	3.08
Left dorsolateral pons	−8	−44	−35	16	4.23
Right spinal trigeminal nucleus	4	−40	−60	19	4.14
Right spinal trigeminal nucleus	8	−38	−47	16	3.74
Regional homogeneity					
Left substantia nigra	−4	−10	−7	112	7.72
Right substantia nigra	12	−18	−5	34	3.96
Right dorsolateral/medial pons	10	−32	−29	17	3.79
Right spinal trigeminal nucleus	4	−46	−55	25	5.33
	8	−38	−47	16	3.74

4. Discussion

Our findings show that individual migraineurs' brainstem function alters through the migraine cycle. In particular, we found significantly greater variability in resting activity in the 24-hour period immediately prior to a migraine attack in brainstem regions that process head pain and that have been shown to be activated during a migraine itself (Afridi et al., 2005a; Denuelle et al., 2007; Weiller et al., 1995). This increase in resting state variability is characterized by increased power at infra-slow frequency ranges and is associated with increased regional homogeneity, a marker of local signal coupling. Since these changes occur immediately prior to a migraine and whilst the individual is *not* in pain, we suggest they are consistent with the idea that brainstem function alters over the migraine cycle. These brainstem functional changes can then lead to a migraine directly via projections to higher cortical areas that can activate head pain, or by facilitating an incoming cerebrovascular trigger to activate higher brain centres resulting in head pain.

Whilst numerous studies have reported that activity increases in areas of the brainstem, including the dorsal pons, during migraine attacks (Afridi et al., 2005a, 2005b; Denuelle et al., 2007; Weiller et al., 1995), few studies have investigated whether functional changes occur in the brainstem immediately prior to a migraine. Of course exploring function prior to a migraine is extremely difficult since it is not possible to predict when a migraine will occur. Whilst the hypothesis that a cerebrovascular trigger is required to initiate a migraine attack has been circulating for many decades (Borsook and Burstein, 2012; Burstein et al., 2015, 2012), more recently it has been proposed that migraine results from dysfunction in subcortical sites which results in the perception of pain from "basal levels of primary traffic" (Goadsby and Akerman, 2012). Others have suggested that brainstem function oscillates and only when the brainstem is in a receptive state can an incoming trigger activate central pathways and evoke head pain (Borsook and Burstein, 2012).

Our findings show that brainstem function alters within a given individual throughout the migraine cycle, specifically in the SpV where trigeminovascular afferents terminate (Noseda and Burstein, 2013), as well as in the dorsolateral/medial pons, an area shown to be activated during a migraine attack. There is also preclinical evidence that trigeminovascular afferents terminate more rostrally in the SpV, in the interpolaris and oralis divisions (Burstein et al., 1998; Davis and Dostrovsky, 1988; Knight et al., 2005) and therefore the dlPons changes reported here may reflect changes in the activity of these more rostral SpV divisions. Strikingly, in both the SpV and dlPons, the variability of resting signal fluctuations immediately prior to a migraine dramatically increased during the 24-hour period prior to a migraine before returning to controls' levels during the interictal period. Indeed, overall brainstem variability in migraineurs is remarkably similar to that in controls with respect to day-to-day fluctuations; however only in migraineurs did dramatic increases occur, and they occurred just before a migraine.

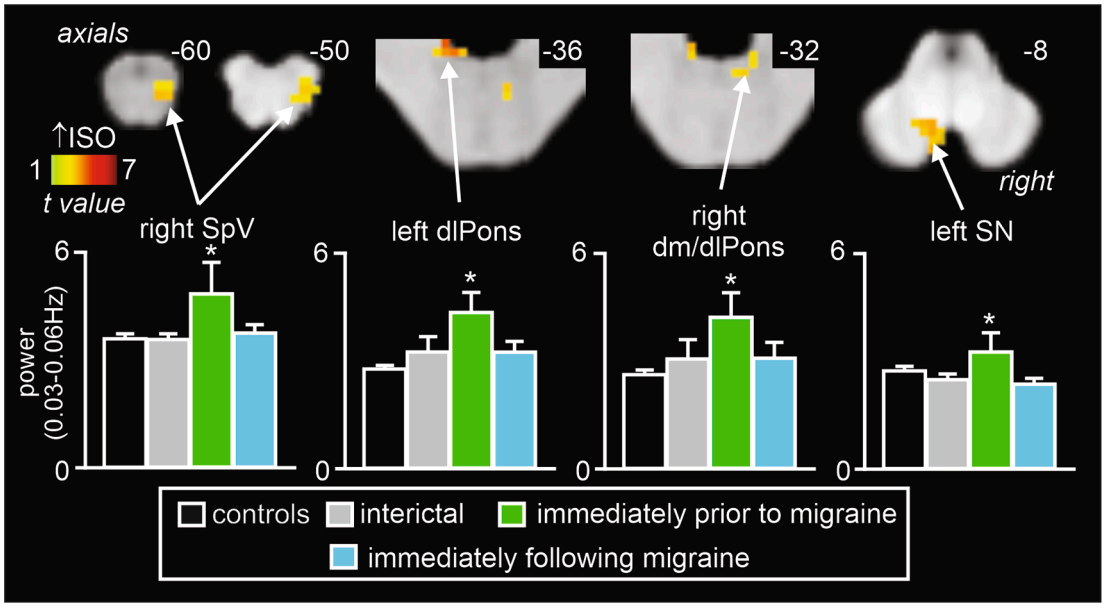

Fig. 2. Significant increases (hot colour scale) in resting infra-slow oscillation (ISO) power (0.03–0.06 Hz) in migraineurs during the 24-hour period prior to the onset of a migraine. Increases are overlaid onto axial slices of a T1-weighted anatomical template of the brainstem. Below are plots of mean (±SEM) ISO power in controls and migraineurs for the right spinal trigeminal nucleus (SpV), left dorsolateral pons (dlPons), right dorsomedial/dorsolateral pons (dm/dlPons) and left substantia nigra (SN). The slice locations in Montreal Neurological Institute space are indicated at the top right of each slice. *p < 0.05 voxel-by-voxel analysis.

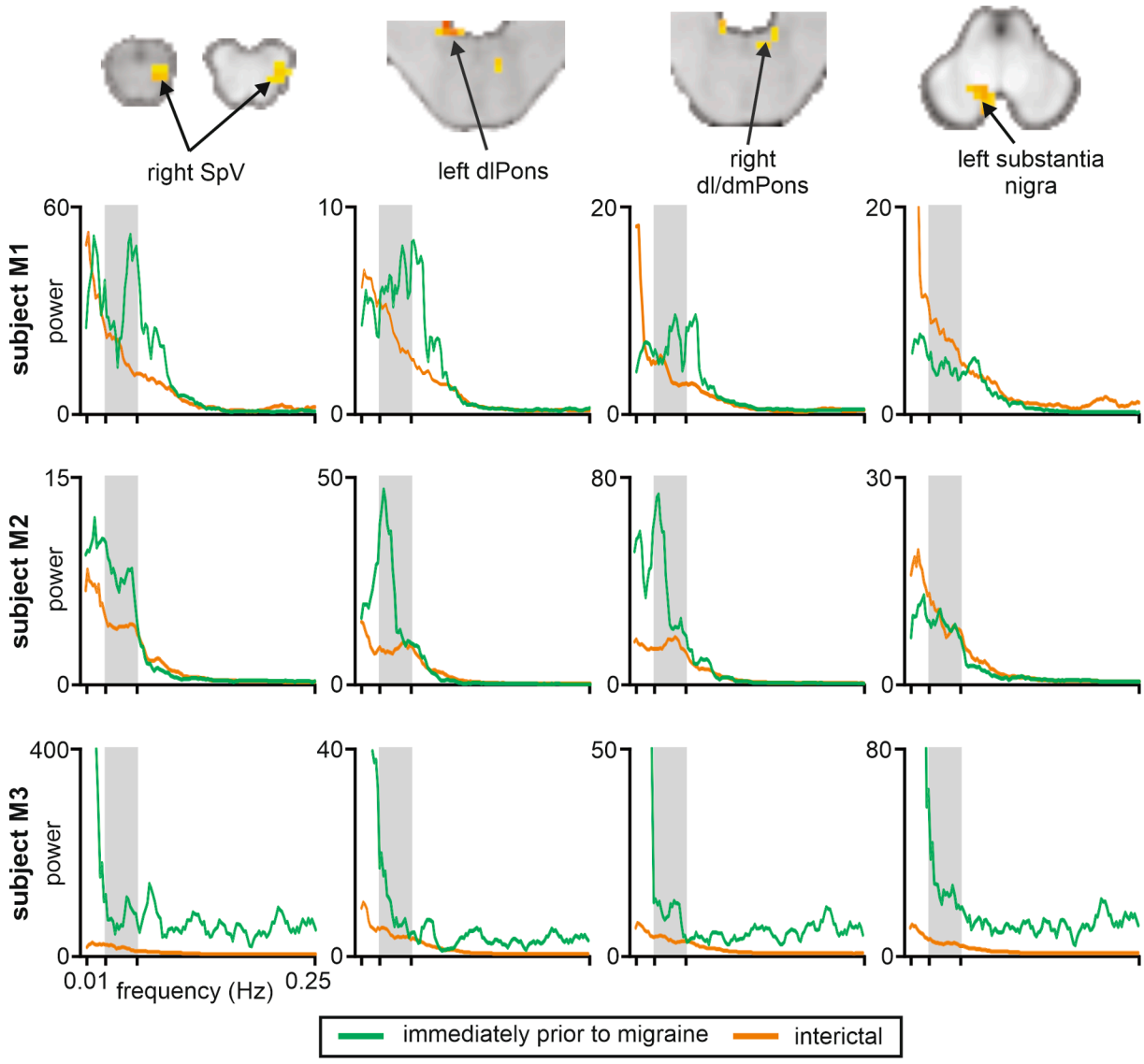

Fig. 3. Plots of power spectra of significant ISO clusters in the three migraineurs (M1, M2, M3). Mean power spectra during the interictal and immediately prior to migraine periods are plotted for each subject for the right spinal trigeminal nucleus (SpV), left dorsolateral pons (dlPons), right dorsomedial/dorsolateral pons (dm/dlPons) and left substantia nigra (SN). Note that particularly for the SpV, dlPons and dm/dlPons, power is greater during the period immediately prior to migraine. These increases encompass the frequency band 0.03–0.06 Hz as indicated by the grey shading.

Importantly, during the period of increased variability, subjects were *not* experiencing head pain, and reported feeling no different to other interictal days. Whilst immediately before a migraine some individuals report fatigue, dizziness and reduced concentration (Giffin et al., 2003), our subjects did not report such changes and the changes in brainstem variability that occurred during this period were not associated with differences in head movements. This supports that the altered resting activity may be a centrally initiated phenomenon, whereby changes occur in the activity of brainstem regions including the SpV, pons and PAG, resulting in the activation of higher cortical regions leading to the experience of head pain. These changes may occur as a result of cyclic oscillations in brainstem function, or may alter for other unknown reasons potentially mediated by dysfunctional hypothalamic activity (Akerman et al., 2011; Drummond and Lance, 1984; Kagan et al., 2013; Meylakh et al., 2018; Schulte et al., 2017), thus ascending to alter levels of basal firing traffic and subsequent activation of central structures leading to head pain (Goadsby and Akerman, 2012).

The increased variability during the 24-hour period immediately preceding a migraine is characterized by increased power at infra-slow frequency ranges and included the frequency band 0.03–0.06 Hz. In addition to previously showing increases in 0.03–0.06 Hz power in migraineurs immediately before a migraine in cross-sectional studies (Meylakh et al., 2018), we have also shown that individuals with chronic trigeminal neuropathic pain display increases in resting 0.03–0.06 Hz oscillations in the trigeminal pain pathway including in the SpV (Alshelh et al., 2016). We have previously hypothesised that increased ISOs at frequencies between 0.03 and 0.06 Hz may reflect increased modulatory activity on local neurons by increased cyclic gliotransmitter release (Halassa et al., 2007; Parri and Crunelli, 2001). Astrocytes display calcium wave oscillations at infra-slow frequency ranges similar to those seen here in migraineurs immediately prior to a migraine and these infra-slow astrocyte calcium waves can propagate among surrounding astrocytes (Crunelli et al., 2002). Indeed, it has been suggested that, in pathological situations, greater numbers of astrocytes may display enhanced calcium wave synchrony, amplitude and NMDA-receptor function (Halassa et al., 2007; Parri and Crunelli, 2001). Furthermore, increased infra-slow oscillations are associated with paroxysmal events and coupled to high frequency power fluctuations in the cortex (Hughes,

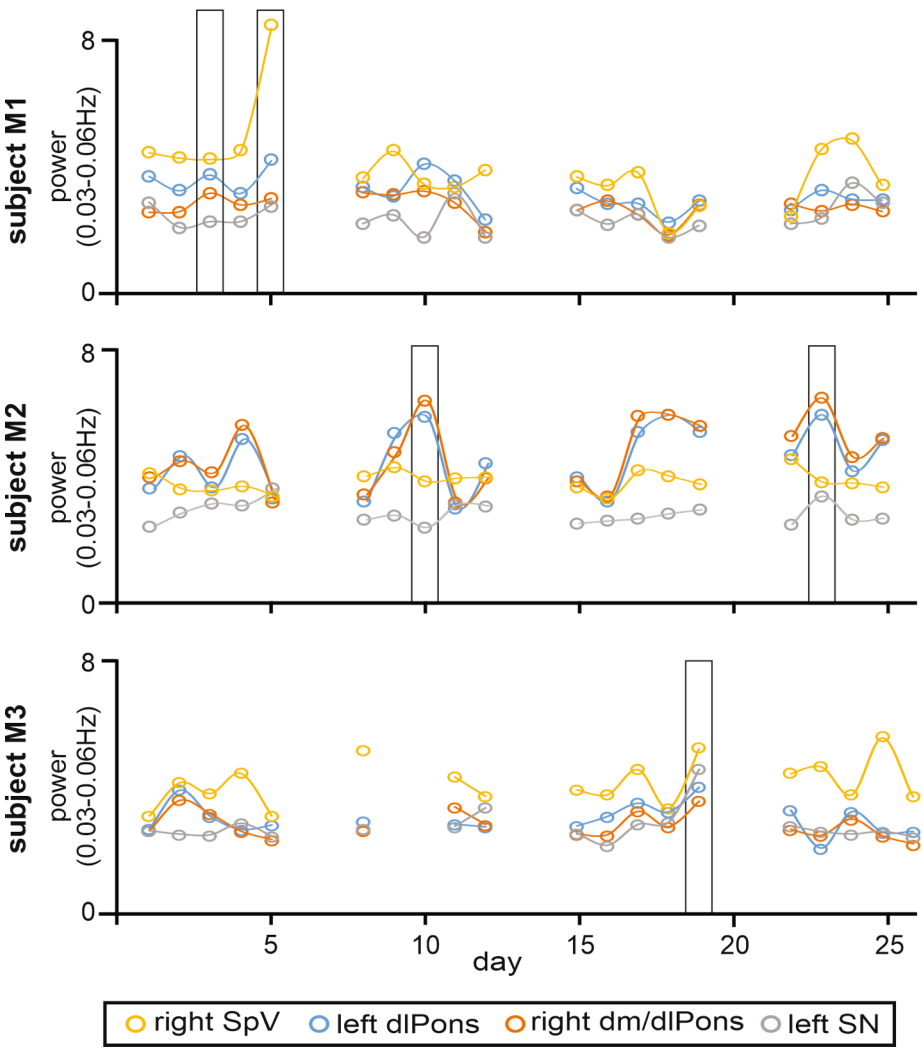

Fig. 4. Plots of daily ISO power (0.03–0.06 Hz) in the three migraineurs (M1, M2, M3). Power is plotted for each subject for the right spinal trigeminal nucleus (SpV), left dorsolateral pons (dlPons), right dorsomedial/dorsolateral pons (dm/dlPons) and left substantia nigra (SN). Note that particularly for the SpV, dlPons and dm/dlPons, power is greater during the period immediately prior to migraine (black box) compared to other days, although there is also some variability in the interictal period. Note for subject M2, migraines occurred in the evening following the "immediately prior to migraine" scans and these migraines resolved by the next morning when "immediately following migraine" scans were collected.

Lorincz, Parri, and Crunelli, 2011; Mantini et al., 2007; Vanhatalo et al., 2004).

Consistent with the idea that astrocytes may modulate neural activity immediately prior to a migraine is our finding of increased regional homogeneity in the same period of the migraine cycle. We found a significant positive relationship between regional homogeneity and infra-slow oscillation power in the SpV and dorsal pons assessed over the entire scanning period. Regional homogeneity evaluates the similarity or synchronization between the time series of a given voxel and its nearest neighbours (Zang et al., 2004). Whilst there is no evidence of a direct relationship between regional homogeneity and astrocytic gliotransmission, the idea that astrocyte activation results in greater and strong synchronicity between astrocytes and thus neighbouring synapses, is consistent with such a positive relationship. Indeed, it has been proposed that calcium oscillation in astrocytes contributes to the propagation of cortical spreading depression (Nedergaard et al., 1995) and evidence from a genetic form of migraine, Familial Hemiplegic Migraine, also points to a critical role of astrocytes in migraine (Benarroch, 2005). More insight into the possible role of astrocytes in migraine can be gathered from neuropathic and inflammatory pain investigations. It has been shown that neuropathic pain is associated with astrocyte activation within regions of the ascending pain pathway (Ji et al., 2013b; Okada-Ogawa et al., 2009; Shi et al., 2012). Given the link between the rhythm of infra-slow oscillations and astrocytes, growing evidence suggests that the origin of these changes takes place in the primary afferent synapse (Alshelh et al., 2016). Such evidence stems from preclinical neuropathic pain models and human post-mortem studies displaying an association between neuropathic pain and astrocyte activation in the dorsal horn/SpV (Garrison et al., 1991; Okada-Ogawa et al., 2009; Shi et al., 2012). Further, in an experimental animal model of neuropathic pain, infra-slow oscillatory activity in the somatosensory thalamus was eliminated by severing the connection between the primary afferent synapse and the thalamus (Iwata et al., 2011). Similarly, altered astrocyte function has also been implicated in trigeminal inflammatory pain models (Shinoda et al., 2020) and is associated with exaggerated nociceptive response to injury or inflammation (Chiang et al., 2011). Indeed, activated astrocytes have been identified in the SpV within one day after induction of trigeminal chronic inflammation as well as trigeminal nerve injury (Guo et al., 2007; Okada-Ogawa et al., 2009; Piao et al., 2006). Furthermore, inhibition of astrocyte activation in the SpV blocks the development of sensitization of SpV nociceptive neurons in the acute tooth pulp inflammatory model (Chiang et al., 2005; Xie et al., 2007). As a result, central changes in astrocyte function in the SpV may play an important role in neuropathic and inflammatory pain conditions, and perhaps in migraine.

Importantly, we found that overall brainstem variability was similar in migraineurs during the interictal period as that of controls, suggesting that migraineurs do not simply have increased signal variability but rather that variability is *specifically altered immediately prior to a migraine attack*. One plausible theory is that altered astrocyte modulation of neural activity within the brainstem drastically changes function which

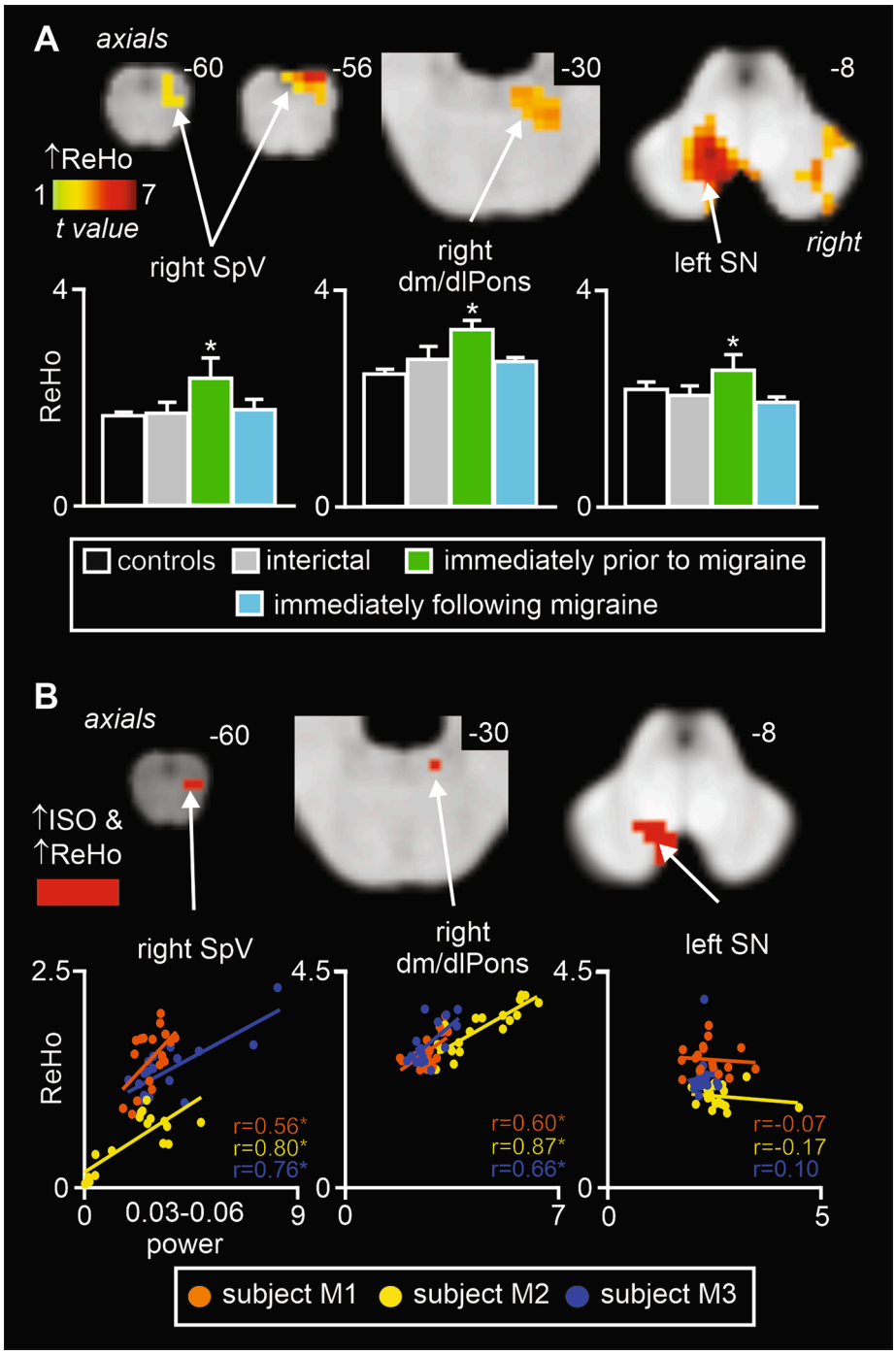

Fig. 5. A: Significant increases (hot colour scale) in resting regional homogeneity (ReHo) in migraineurs during the 24-hour period prior to the onset of a migraine. Increases are overlaid onto axial slices of a T1-weighted anatomical template of the brainstem. Below are plots of mean (±SEM) ReHo in controls and migraineurs for the right spinal trigeminal nucleus (SpV), right dorsomedial/dorsolateral pons (dm/dlPons) and left substantia nigra (SN). The slices locations in Montreal Neurological Institute space are indicated at the top right of each slice. *p < 0.05 voxel-by-voxel analysis. **B:** Areas in which ReHo and infra-slow oscillation (ISO) power were increased during the period immediately prior to a migraine (red colour shading). Below are plots of ReHo against ISO power for each cluster in each of the three migraineurs (M1, M2, M3). Note that for the right SpV and right dm/dlPons ReHo and ISO were significantly positively correlated in all three migraineurs. *p < 0.05 Pearsons correlation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

then either triggers a migraine itself or provides a permissive brainstem state so that an external cerebrovascular trigger can activate higher brain centres and initiate a migraine attack. Interestingly, we recently found that in the 24-hour period before a migraine, the perceived intensity of acute noxious orofacial stimuli are diminished, which appears contrary to the idea that immediately prior to a migraine the brainstem becomes more permissive to incoming orofacial stimuli (Marciszewski et al., 2018). Therefore, it is possible that astrocytic activity in migraine conditions is similar to what has been found to occur in neuropathic and inflammatory pain models, however in the case of the migraine this activity, particularly within the SpV, is more transient, thus only occurring within 24 h preceding a migraine attack. This requires further exploration.

Whilst this is the first study to explore resting signal fluctuations in the brainstem over the migraine cycle in individual subjects, three previous studies have explored functional activity over the migraine cycle. In a case study of one migraineur over the course of 30 days, Schulte and May (Schulte and May, 2016) reported that during the period immediately prior to a migraine, greater functional coupling occurred between the hypothalamus and SpV, whilst during a migraine attack, greater functional coupling occurred between the hypothalamus and dorsal rostral pons. While we did not explore hypothalamic function in the current study, these coupling changes are consistent with our data in that brainstem function changes in the period immediately prior to a migraine. If, for example, such functional changes are related to altered astrocyte modulation of local neural function, it may be possible to

prevent a migraine from occurring by preventing such astrocyte changes. Furthermore, Schulte and May (Schulte et al., 2020b) later corroborated their findings by demonstrating increased functional connectivity between the nucleus accumbens and dorsal rostral pons during the period immediately prior to a migraine. In addition, they also found that activation of the hypothalamus was present within 48 h prior to a migraine headache following painful trigeminal stimulation (Schulte et al., 2020a). Therefore, the findings from the current study support that functional activity is altered in the period immediately prior to a migraine headache.

Given the consistency between the results of this longitudinal study and our previous cross-sectional studies we are confident that our findings are robust. However, there are several important limitations to note. Firstly, since we focussed on the brainstem we have not provided any insight into diencephalic or higher cortical areas in this present study, though we are aware of the importance of these regions in migraine. Secondly, despite using spatial normalization techniques designed specifically for the brainstem, given the relatively low spatial resolution of resting state fMRI and the intricate parcellation of the brainstem, some clusters likely encompass multiple brainstem regions. Thirdly, due to the difficulty of recruiting patients with the availability or willingness to perform multiple MRI sessions we were only able to recruit three migraineurs and five controls. Given this, we were not able to determine potential age and gender effects, although age and gender were not different between groups. Whilst we were also not able to robustly determine laterality effects with respect to migraine headache side, we did find that the ISO power changes within the SpV and dlPons were related to the side of subsequent migraine. Furthermore, the migraine subjects in the current study experienced very few migraine attacks, thus these data require confirmation from patients with higher migraine frequency. Additional subjects and migraine events would provide the opportunity to explore the relationship between migraine severity and changes in brainstem function. Finally, one subject was taking selective serotonin reuptake inhibitors which might have influenced the resting activity in this subject, thus impacting the results. Again, recruiting a larger population of patients would help to validate the findings. Nevertheless, the large number of repeated measures per subject, together with the corroboration by our previous cross-sectional studies, helps to ensure the findings are robust.

The findings of this study clearly show that resting brainstem function fluctuates over the migraine cycle in a given individual, with functional changes reflected particularly in the period immediately preceding a migraine. We suggest that this change in brainstem function could result from altered synaptic transmission evoked by increased gliotransmission, which could evoke a migraine by either an increase in basal firing or by creating a permissive state whereby an external trigger can activate trigeminal pain pathways. These data provide a target timeframe and biological process for prophylactic treatments for migraine. Whether this includes novel treatments targeting gliotransmission remains to be seen. To understand this further, studies investigating the role of human glia in pain control is imperative (Ji et al., 2013a).

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

Afridi, S.K., Giffin, N.J., Kaube, H., Friston, K.J., Ward, N.S., Frackowiak, R.S., Goadsby, P.J., 2005a. A positron emission tomographic study in spontaneous migraine. Arch. Neurol. 62 (8), 1270–1275. https://doi.org/10.1001/archneur.62.8.1270.

Afridi, S.K., Matharu, M.S., Lee, L., Kaube, H., Friston, K.J., Frackowiak, R.S., Goadsby, P. J., 2005b. A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. Brain 128 (Pt 4), 932–939. https://doi.org/10.1093/brain/awh416.

Akerman, S., Holland, P.R., Goadsby, P.J., 2011. Diencephalic and brainstem mechanisms in migraine. Nat. Rev. Neurosci. 12 (10), 570–584. https://doi.org/10.1038/nrn3057.

Alshelh, Z., Di Pietro, F., Youssef, A.M., Reeves, J.M., Macey, P.M., Vickers, E.R., Peck, C. C., Murray, G.M., Henderson, L.A., 2016. Chronic neuropathic pain: it's about the rhythm. J. Neurosci. 36 (3), 1008–1018. https://doi.org/10.1523/JNEUROSCI.2768-15.2016.

Bahra, A., Matharu, M.S., Buchel, C., Frackowiak, R.S., Goadsby, P.J., 2001. Brainstem activation specific to migraine headache. Retrieved from Lancet 357 (9261), 1016–1017. http://www.ncbi.nlm.nih.gov/pubmed/11293599.

Benarroch, E.E., 2005. Neuron-astrocyte interactions: partnership for normal function and disease in the central nervous system. Mayo Clin. Proc. 80 (10), 1326–1338. https://doi.org/10.4065/80.10.1326.

Bernstein, C., Burstein, R., 2012. Sensitization of the trigeminovascular pathway: perspective and implications to migraine pathophysiology. J. Clin. Neurol. 8 (2), 89–99. https://doi.org/10.3988/jcn.2012.8.2.89.

Borsook, D., Burstein, R., 2012. The enigma of the dorsolateral pons as a migraine generator. Cephalalgia 32 (11), 803–812. https://doi.org/10.1177/0333102412453952.

Burstein, R., Yamamura, H., Malick, A., Strassman, A.M., 1998. Chemical stimulation of the intracranial dura induces enhanced responses to facial stimulation in brain stem trigeminal neurons. J. Neurophysiol. 79 (2), 964–982. https://doi.org/10.1152/jn.1998.79.2.964.

Burstein, R., Strassman, A., Moskowitz, M., 2012. Can cortical spreading depression activate central trigeminovascular neurons without peripheral input? Pitfalls of a new concept. Cephalalgia 32 (6), 509–511. https://doi.org/10.1177/0333102411436262.

Burstein, R., Noseda, R., Borsook, D., 2015. Migraine: multiple processes, complex pathophysiology. J. Neurosci. 35 (17), 6619–6629. https://doi.org/10.1523/JNEUROSCI.0373-15.2015.

Chiang, C.Y., Zhang, S., Xie, Y.F., Hu, J.W., Dostrovsky, J.O., Salter, M.W., Sessle, B.J., 2005. Endogenous ATP involvement in mustard-oil-induced central sensitization in trigeminal subnucleus caudalis (Medullary Dorsal Horn). J. Neurophysiol. 94 (3), 1751–1760. https://doi.org/10.1152/jn.00223.2005.

Chiang, C.Y., Dostrovsky, J.O., Iwata, K., Sessle, B.J., 2011. Role of glia in orofacial pain. Neuroscientist 17 (3), 303–320. https://doi.org/10.1177/1073858410386801.

Chudler, E.H., Dong, W.K., 1995. The role of the basal ganglia in nociception and pain. Retrieved from Pain 60 (1). https://journals.lww.com/pain/Fulltext/1995/01000/The_role_of_the_basal_ganglia_in_nociception_and.2.aspx.

DaSilva, A.F.M., Becerra, L., Makris, N., Strassman, A.M., Gonzalez, R.G., Geatrakis, N., Borsook, D., 2002. Somatotopic activation in the human trigeminal pain pathway. The Journal of Neuroscience 22 (18), 8183–8192. https://doi.org/10.1523/JNEUROSCI.22-18-08183.2002.

Davis, K.D., Dostrovsky, J.O., 1988. Responses of feline trigeminal spinal tract nucleus neurons to stimulation of the middle meningeal artery and sagittal sinus. J. Neurophysiol. 59 (2), 648–666. https://doi.org/10.1152/jn.1988.59.2.648.

Denuelle, M., Fabre, N., Payoux, P., Chollet, F., Geraud, G., 2007. Hypothalamic activation in spontaneous migraine attacks. Headache 47 (10), 1418–1426. https://doi.org/10.1111/j.1526-4610.2007.00776.x.

Diedrichsen, J., 2006. A spatially unbiased atlas template of the human cerebellum. Neuroimage 33 (1), 127–138.

Drummond, P.D., Lance, J.W., 1984. Neurovascular disturbances in headache patients. Clin. Exp. Neurol. 20, 93–99.

Fields, H.L., Heinricher, M.M., 1985. Anatomy and physiology of a nociceptive modulatory system. Philos. Trans. R. Soc. Lond. B Biol. Sci. 308 (1136), 361–374. https://doi.org/10.1098/rstb.1985.0037.

Friston, K.J., Holmes, A.P., Poline, J.B., Grasby, P.J., Williams, S.C., Frackowiak, R.S., Turner, R., 1995. Analysis of fMRI time-series revisited. Neuroimage 2 (1), 45–53. https://doi.org/10.1006/nimg.1995.1007.

Garrison, C.J., Dougherty, P.M., Kajander, K.C., Carlton, S.M., 1991. Staining of glial fibrillary acidic protein (GFAP) in lumbar spinal cord increases following a sciatic nerve constriction injury. Brain Res. 565 (1), 1–7. https://doi.org/10.1016/0006-8993(91)91729-k.

Giffin, N.J., Ruggiero, L., Lipton, R.B., Silberstein, S.D., Tvedskov, J.F., Olesen, J., Altman, J., Goadsby, P.J., Macrae, A., 2003. Premonitory symptoms in migraine: an electronic diary study. Neurology 60 (6), 935–940.

Goadsby, P.J., Akerman, S., 2012. The trigeminovascular system does not require a peripheral sensory input to be activated–migraine is a central disorder. Focus on 'Effect of cortical spreading depression on basal and evoked traffic in the trigeminovascular sensory system'. Cephalalgia 32 (1), 3–5. https://doi.org/10.1177/0333102411430267.

Guo, W., Wang, H., Watanabe, M., Shimizu, K., Zou, S., LaGraize, S.C., Wei, F., Dubner, R., Ren, K., 2007. Glial–Cytokine–Neuronal interactions underlying the

mechanisms of persistent pain. J. Neurosci. 27 (22), 6006–6018. https://doi.org/10.1523/JNEUROSCI.0176-07.2007.
Halassa, M.M., Fellin, T., Haydon, P.G., 2007. The tripartite synapse: roles for gliotransmission in health and disease. Trends Mol. Med. 13 (2), 54–63. https://doi.org/10.1016/j.molmed.2006.12.005.
S.W. Hughes M.L. Lorincz H.R. Parri V. Crunelli Infraslow (<0.1 Hz) oscillations in thalamic relay nuclei basic mechanisms and significance to health and disease states Prog Brain Res 193 2011 145 162 10.1016/B978-0-444-53839-0.00010-7 B978-0-444-53839-0.00010-7 [pii].
Iwata, M., LeBlanc, B.W., Kadasi, L.M., Zerah, M.L., Cosgrove, R.G., Saab, C.Y., 2011. High-frequency stimulation in the ventral posterolateral thalamus reverses electrophysiologic changes and hyperalgesia in a rat model of peripheral neuropathic pain. Pain 152 (11), 2505–2513. https://doi.org/10.1016/j.pain.2011.07.011.
Ji, R.-R., Berta, T., Nedergaard, M., 2013a. Glia and pain: is chronic pain a gliopathy? PAIN® 154, S10–S28. https://doi.org/10.1016/j.pain.2013.06.022.
Ji, X.-T., Qian, N.-S., Zhang, T., Li, J.-M., Li, X.-K., Wang, P., Zhao, D.-S., Huang, G., Zhang, L., Fei, Z., Jia, D., Niu, L.e., Gallyas, F., 2013b. Spinal astrocytic activation contributes to mechanical allodynia in a rat chemotherapy-induced neuropathic pain model. PLoS ONE 8 (4), e60733. https://doi.org/10.1371/journal.pone.0060733.
Kagan, R., Kainz, V., Burstein, R., Noseda, R., 2013. Hypothalamic and basal ganglia projections to the posterior thalamus: possible role in modulation of migraine headache and photophobia. Neuroscience 248, 359–368. https://doi.org/10.1016/j.neuroscience.2013.06.014.
Knight, Y.E., Classey, J.D., Lasalandra, M.P., Akerman, S., Kowacs, F., Hoskin, K.L., Goadsby, P.J., 2005. Patterns of fos expression in the rostral medulla and caudal pons evoked by noxious craniovascular stimulation and periaqueductal gray stimulation in the cat. Brain Res. 1045 (1), 1–11. https://doi.org/10.1016/j.brainres.2005.01.091.
Macey, P.M., Macey, K.E., Kumar, R., Harper, R.M., 2004. A method for removal of global effects from fMRI time series. Retrieved from Neuroimage 22 (1), 360–366. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15110027.
Mai, J.K., Paxinos, G., Voss, T., 2007. Atlas of the Human Brain, (3rd ed.). Academic Press.
Mantini, D., Perrucci, M. G., Del Gratta, C., Romani, G. L., & Corbetta, M. (2007). Electrophysiological signatures of resting state networks in the human brain. Proc Natl Acad Sci U S A, 104(32), 13170-13175. doi:0700668104 [pii] 10.1073/pnas.0700668104.
Marciszewski, K.K., Meylakh, N., Di Pietro, F., Mills, E.P., Macefield, V.G., Macey, P.M., Henderson, L.A., 2018. Changes in brainstem pain modulation circuitry function over the migraine cycle. J. Neurosci. 38 (49), 10479–10488. https://doi.org/10.1523/JNEUROSCI.1088-18.2018.
Matharu, M.S., Bartsch, T., Ward, N., Frackowiak, R.S., Weiner, R., Goadsby, P.J., 2004. Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain 127 (Pt 1), 220–230. https://doi.org/10.1093/brain/awh022.
Meylakh, N., Marciszewski, K.K., Di Pietro, F., Macefield, V.G., Macey, P.M., Henderson, L.A., 2018. Deep in the brain: changes in subcortical function immediately preceding a migraine attack. Hum. Brain Mapp. 39 (6), 2651–2663. https://doi.org/10.1002/hbm.v39.610.1002/hbm.24030.
Nedergaard, M., Cooper, A.J.L., Goldman, S.A., 1995. Gap junctions are required for the propagation of spreading depression. J. Neurobiol. 28 (4), 433–444. https://doi.org/10.1002/(ISSN)1097-469510.1002/neu.v28:410.1002/neu.480280404.
Noseda, R., Burstein, R., 2013. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. Pain 154 (Suppl), 1. https://doi.org/10.1016/j.pain.2013.1007.1021. doi:10.1016/j.pain.2013.07.021.
Okada-Ogawa, A., Suzuki, I., Sessle, B.J., Chiang, C.-Y., Salter, M.W., Dostrovsky, J.O., Tsuboi, Y., Kondo, M., Kitagawa, J., Kobayashi, A., Noma, N., Imamura, Y., Iwata, K., 2009. Astroglia in medullary dorsal horn (Trigeminal Spinal Subnucleus Caudalis) are involved in trigeminal neuropathic pain mechanisms. J. Neurosci. 29 (36), 11161–11171. https://doi.org/10.1523/JNEUROSCI.3365-09.2009.
Ossipov, M.H., Dussor, G.O., Porreca, F., 2010. Central modulation of pain. J. Clin. Investig. 120 (11), 3779–3787. https://doi.org/10.1172/JCI43766.
Parri, H.R., Crunelli, V., 2001. Pacemaker calcium oscillations in thalamic astrocytes in situ. Retrieved from NeuroReport 12 (18), 3897–3900. http://www.ncbi.nlm.nih.gov/pubmed/11742206.
Paxinos, G., Huang, X., 1995. Atlas of the Human Brainstem, 1st ed. Academic Press, San Diego.
Piao, Z. G., Cho, I.-H., Park, C. K., Hong, J. P., Choi, S.-Y., Lee, S. J., . . . Oh, S. B. (2006). Activation of glia and microglial p38 MAPK in medullary dorsal horn contributes to tactile hypersensitivity following trigeminal sensory nerve injury. Pain, 121(3), 219-231. doi:https://doi.org/10.1016/j.pain.2005.12.023.
Särkkä, S., Solin, A., Nummenmaa, A., Vehtari, A., Auranen, T., Vanni, S., Lin, F.-H., 2012. Dynamic retrospective filtering of physiological noise in BOLD fMRI: DRIFTER. Neuroimage 60 (2), 1517–1527. https://doi.org/10.1016/j.neuroimage.2012.01.067.
Schulte, L.H., Allers, A., May, A., 2017. Hypothalamus as a mediator of chronic migraine: evidence from high-resolution fMRI. Neurology 88 (21), 2011–2016. https://doi.org/10.1212/wnl.0000000000003963.
Schulte, L.H., May, A., 2016. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. Brain 139 (Pt 7), 1987–1993. https://doi.org/10.1093/brain/aww097.
Schulte, L.H., Mehnert, J., May, A., 2020a. Longitudinal neuroimaging over 30 Days: temporal characteristics of migraine. Ann. Neurol. 87 (4), 646–651. https://doi.org/10.1002/ana.25697.
Schulte, L.H., Menz, M.M., Haaker, J., May, A., 2020b. The migraineur's brain networks: continuous resting state fMRI over 30 days. Cephalalgia 40 (14), 1614–1621. https://doi.org/10.1177/0333102420951465.
Shi, Y., Gelman, B.B., Lisinicchia, J.G., Tang, S.J., 2012. Chronic-pain-associated astrocytic reaction in the spinal cord dorsal horn of human immunodeficiency virus-infected patients. J. Neurosci. 32 (32), 10833–10840. https://doi.org/10.1523/jneurosci.5628-11.2012.
Shinoda, M., Hayashi, Y., Kubo, A., Iwata, K., 2020. Pathophysiological mechanisms of persistent orofacial pain. J. Oral Sci. 62 (2), 131–135. https://doi.org/10.2334/josnusd.19-0373.
Vanhatalo, S., Palva, J.M., Holmes, M.D., Miller, J.W., Voipio, J., Kaila, K., 2004. Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. Proc. Natl. Acad. Sci. U.S.A. 101 (14), 5053–5057. https://doi.org/10.1073/pnas.03053751015375101.
Weiller, C., May, A., Limmroth, V., Juptner, M., Kaube, H., Schayck, R.V., Diener, H.C., 1995. Brain stem activation in spontaneous human migraine attacks. Retrieved from Nat. Med. 1 (7), 658–660. http://www.ncbi.nlm.nih.gov/pubmed/7585147.
Xie, Y.F., Zhang, S., Chiang, C.Y., Hu, J.W., Dostrovsky, J.O., Sessle, B.J., 2007. Involvement of glia in central sensitization in trigeminal subnucleus caudalis (medullary dorsal horn). Brain Behav. Immun. 21 (5), 634–641. https://doi.org/10.1016/j.bbi.2006.07.008.
Zang, Y., Jiang, T., Lu, Y., He, Y., Tian, L., 2004. Regional homogeneity approach to fMRI data analysis. Neuroimage 22 (1), 394–400. https://doi.org/10.1016/j.neuroimage.2003.12.030.