

# **Resting State fMRI Frequency Specific Alterations In Primary Headache Disorders**

## **PhD Thesis**

Péter Faragó, M.D.

Clinical and Experimental Neuroscience Program,

Doctoral School of Clinical Medicine,

Faculty of Medicine, University of Szeged

Supervisor: Zsigmond Tamás Kincses, M.D., Ph.D.

Department of Neurology, Albert Szent-Györgyi Clinical Center,

University of Szeged

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- I. **Péter Faragó**, Nikoletta Szabó, Eszter Tóth, Bernadett Tuka, András Király, Gergő Csete, Árpád Párdutz, Délia Szok, János Tajti, Csaba Ertsey, László Vécsei, Zsigmond Tamás Kincses: Ipsilateral Alterations of Resting State Activity Suggests That Cortical Dysfunction Contributes to the Pathogenesis of Cluster Headache. Brain Topography. 2016. Oct., DOI 10.1007/s10548-016-0535-x

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- I. András Király, Nikoletta Szabó, Eszter Tóth, Gergő Csete, **Péter Faragó**, Krisztián Kocsis, Anita Must, László Vécsei, Zsigmond Tamás Kincses: Male brain ages faster: the age and gender dependence of subcortical volumes. Brain imaging and behaviour 2016. Sep. DOI 10.1007/s11682-015-9468-3.

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## Abbreviations:

BET	brain extraction toolkit
BOLD	blood oxygen level dependent
CH	cluster headache
CGRP	calcitonin gene related peptide
CSD	cortical spreading depression
DOF	degree of freedom
DTI	diffusion tensor imaging
EEG	electroencephalography
EPI	echo planar imaging
FEAT	FMRI Expert Analysis Tool
fMRI	functional magnetic resonance imaging
FLIRT	FMRIB's Linear Registration Toolkit
FNIRT	FMRIB's Nonlinear Registration Toolkit
FSL	FMRIB's Software Toolkit
GLM	general linear model
MELODIC	multivariate exploratory linear optimized decomposition into independent components
MEG	magnetoencephalography
MRI	magnetic resonance imaging
MWoA	migraine without aura
MWA	migraine with aura

PACAP-38	pituitary adenylate cyclase activating polypeptide
PET	positron emission tomography
RSN	resting state network
SUSAN	smallest univalue segment assimilating nucleus
TBSS	tract-based spatial statistics
TFCE	threshold free cluster enhancement
TMS	transcranial magnetic stimulation
VBM	voxel based morphometry
VEP	visual evoked potentials
VIP	vasoactive intestinal polypeptide

## Summary

### Introduction

The functional MRI imaging is a well-known method to analyse the functional connections in the brain, and a basic element of the MRI based neuroscience.

### Aims

Our aim was to analyse the functional connectivity of the resting state network not just in the whole, but in well-separated frequency bands in primary headache disorders. Furthermore, we aimed to examine not just the functional connectivity of the networks, but the amplitude of fluctuation in each network and also in the whole brain independently.

### Methods

17 patients with cluster headache and 51 migraine patients (18 with aura (MWA), 33 without aura (MWOA)) were recruited. The control groups included 26 and 32 (respectively) healthy, age-matched volunteer controls with no history of any neurological or psychiatric diseases. T1 and resting state images were acquired from all participants. After the preprocessing the resting state networks were calculated. The time series of the network were decomposed into 5 frequency bands, the new and the original time courses were regressed back to the images of the individuals to calculate a frequency and the individual specific networks. The calculated networks were compared by nonparametric permutation test.

The mean amplitude of the frequency specific time series were calculated for each network. The network's mean time courses were compared by a two sample T-test. The mean amplitude estimation was performed voxelwise and compared between the groups.

### Results

The CH group showed increased functional connectivity compared to the healthy controls in all cases. The left sided dataset showed increased connectivity in the left attention network at higher frequencies (0.08-0.04 Hz) and in the cerebellar network at lower frequencies (0.02-0.01



Hz). The right sided dataset showed increased connectivity in the right attention network and also in the cerebellar network at same frequencies as the left sided dataset. The original dataset showed increased connectivity in both the attention and also in the cerebellar network. Furthermore, the functional connectivity showed correlation with the cumulative headache days.

No functional connectivity changes were measured between the migraine groups and healthy controls. There was no significant difference between MWA and healthy controls. Increased amplitude of fluctuation was detected between the MWA and the MWoA group in all investigated networks. Higher amplitude was measured in the MWA group at the 0.08-0.04 Hz frequency band. The voxel-wise comparison showed increased amplitude in the MWA group compared to MWoA group. Between MWoA patients and the healthy controls, the default mode network showed decreased amplitude in the MWoA group at the 0.04-0.02 Hz frequency band.

## Discussion

Our results revealed resting state fMRI changes in primary headache disorders compared to the healthy controls. The changes were found in the functional connectivity and also in the amplitude of fluctuation in separated frequency bands. Furthermore, the resulted areas strictly connected to the headache side in CH. The resulted areas could be the part of the “pain matrix”. These results provide a deeper insight into the patomechanism of migraine and CH. Furthermore, these results help us to understand better their connection to the pain processing system.

## Introduction

### *Cluster headache*

#### **Symptoms and epidemiology**

The cluster headache (CH), a trigeminal autonomic headache, is one of the most painful primary headache disorder. The headache is characterized by severe, strictly unilateral, retro-orbital pain, which is associated with autonomic neurological symptoms at the side of the headache (lacrimation, rhinorrhoea, conjunctival injection, flush) (Bes et al., 2013). The pain lasts for 15-180 minutes, appears several times in a day and the headache periods (clusters) can last several weeks or months followed by a long headache-free period. The cluster periods notably follow a circadian pattern, the patients usually know the interval and the onset of the headaches. The headache is strictly unilateral, never appears on the other side or both sides. The localisation of the symptoms suggests a trigemino-vascular origin. The well-known risk factors of CH are smoking, alcohol usage and positive family history. The CH mainly starts between the age of 20 and 50 and mostly affects males. The prevalence is about 1% without ethnic preference (Geweke, 2002). Although, CH is one of the rarest primary headache disorders, it usually causes severe headache, which causes extended disability, which could interfere with the patient's regular daily activity.

#### **Pathology, pathomechanism**

The pathomechanism of CH is not fully understood yet. The hypotheses about the pathomechanism are based on the following features of the disease: (i) circadian rhythmicity, (ii) trigeminal appearance of the pain and (iii) autonomic neurological symptoms. One of these theories is about the inflammation of the cavernous sinus, which in turn stimulates the trigeminal C fibres and the sympathetic fibres (Hardebo, 1991). The periodic appearance, the seasonal activity suggests the role of the hypothalamus in the pathomechanism of the CH. Altered fluctuation of melatonin synthesis, the abnormal circadian rhythmicity and hormonal dysfunction also strengthened this hypothesis (Chazot et al., 1984; Ferrari et al., 1983).

Hypothalamic stimulation (Leone et al., 2001), as a possibly effective treatment of the disease, also confirmed the hypothalamic origin.

Neuropeptide serum concentrations were also showed to be altered in CH, similarly to migraine. Calcitonin gene-related polypeptide (CGRP) and vasoactive intestinal polypeptide (VIP) levels are increased during headache, but become normal after oxygen therapy (Goadsby and Edvinsson, 1994). Decreased pituitary adenylate cyclase activating polypeptide-38 (PACAP-38) level was reported between the headache periods (Tuka et al., 2016).

### **Imaging biomarkers of cluster headache**

One thing what imaging studies repeatedly confirmed about CH was the involvement of hypothalamus. Positron emission tomography studies showed higher activation in the ipsilateral hypothalamus during cluster headache attacks (May et al., 1998). FMRI functional connectivity studies also support the higher activation in the hypothalamus (May et al., 2000; Morelli et al., 2009). Resting state fMRI studies found altered functional connectivity between the hypothalamus and several other brain structures such as the anterior thalamus, ipsilateral basal ganglia, insula, cingulate cortex or the medial frontal gyrus (Qiu et al., 2015a; Qiu et al., 2013; Rocca et al., 2010; Yang et al., 2014) e.g. the elements of the pain matrix (according to Tracey: “large distributed brain network [activity] during nociceptive processing” (Sprenger et al., 2007; Tracey, 2008)). Other than these studies, there is still no evidence for altered activity of the resting state networks (RSN) in CH. However this could be expected from those results showing cortical hyperexcitability in CH (Cosentino et al., 2015).

Structural imaging studies also pointed out the importance of the hypothalamus in CH. VBM studies found increased grey matter density in hypothalamus in CH compared to healthy individuals (Arkink et al., 2017; May et al., 1999). However there were other investigations, which were unable to replicate these results (Absinta et al., 2012; Yang et al., 2013). These studies also showed loss of the grey matter volume in various structures of the above mentioned pain matrix during pain free periods in CH (Absinta et al., 2012; Yang et al., 2013). Our and another diffusion tensor imaging (DTI) investigation revealed an extensive white matter microstructural alterations in interictal periods (Szabo et al., 2013; Teepker et al., 2012).

In our earlier study, we proposed that these alterations in the grey as well as in the white matter might be the result of parallel maladaptive plasticity and degenerative changes.

## Therapy

The headache in the acute phase could be treated by non-steroid painkillers. Pure oxygen inhalation, local or intranasal anaesthetics (e.g.: lidocaine) or triptans are effective in the acute phase of CH (Robbins et al., 2016).

Treatment	Efficacy	Recommendation
Sumatriptan (subcutaneous)	6 mg	Level A: established as effective
Zolmitriptan (nasal spray)	5 mg and 10 mg	Level A: established as effective
Oxygen	100% 6-12 L/min	Level A: established as effective
Sumatriptan (nasal spray)	20 mg	Level B: probably effective
Zolmitriptan (oral)	5 mg and 10 mg	Level B: probably effective
Sphenopalatine ganglion stimulation	NA	Level B: probably effective
Cocaine/lidocaine (nasal spray)	10% -10%	Level C: possibly effective
Octreotide (subcutaneous)	100 mg	Level C: possibly effective

*Table 1.* Acute Therapy of Cluster Headache modified from The American Headache Society Evidence-Based Guidelines (Robbins et al., 2016).

Calcium channel blockers (e.g.: verapamil), ergot-alkaloids, corticosteroids, tricyclic antidepressants, antiepileptic drugs (e.g.: valproate) and also triptans are used for interval therapy. According to the Guideline of the American Headache Society the sphenopalatine ganglion stimulation can also be an effective treatment in the cluster attack (Robbins et al., 2016).

<b>Treatment</b>	<b>Study Population</b>	<b>Efficacy</b>	<b>Recommendation</b>
Suboccipital steroid injection	Episodic and chronic CH	Suboccipital single injection or injection series with corticosteroids is effective in reducing attack frequency	Level A: established as effective
Civamide‡ (nasal spray)	Episodic and chronic CH	100 mL of 0.025% civamide in each nostril daily is effective in reducing attack frequency	Level B: probably effective
Lithium	Episodic and chronic CH	Lithium 900 mg is effective in reducing attack frequency	Level C: possibly effective
Verapamil	Episodic and chronic CH	Verapamil 360 mg daily is effective in reducing attack frequency	Level C: possibly effective
Warfarin	Refractory chronic CH	Warfarin daily with International Normalized Ratio goal of 1.5 to 1.9 is effective in reducing attack frequency	Level C: possibly effective
Melatonin	Episodic and chronic CH	Melatonin 10 mg every evening is effective in reducing attack frequency	Level C: possibly effective

*Table 2.* Prophylactic Therapy of Cluster Headache according to (Robbins et al., 2016).

In chronic form of the disease, surgical intervention should be needed. There are some evidence that occipital nerve blockade (Kinfel et al., 2015; Lambru et al., 2014) or local nerve stimulation (Miller et al., 2017; Mueller et al., 2013) could be effective in CH interval therapy. Deep brain stimulation of the hypothalamus is also a possible treatment in chronic form of CH (Leone et al., 2001). Despite the several possible treatments, unfortunately there is still no highly effective preventive therapy of CH in our hand.

## *Migraine*

### **Symptoms and epidemiology**

Migraine is the most common primary headache disorder and also the most common disabling headache disease. The incidence of the disease is about 10% of the whole adult population (Lipton et al., 1997), and it is two or three times more common among women (Smitherman et al., 2013). The headache mostly starts in young adulthood. The migraine attacks could be provoked by environmental factors, such as specific foods or drinks, smoking or strong smell, stress situation and anxiety (Pellegrino et al., 2017). Menstruation is a very common provoking factor among women (Allais et al., 2018). While the disease is not life threatening it significantly influences the quality of life and has an enormous economic burden.

The migraine attack can be separated into four phases. The first part of attack is mostly a *prodromal phase*. This phase starts several hours, even a day before the actual headache. The symptoms of this phase are not well specified. The patients may experience irritability, depression, anxiety, increased hunger or thirst. The prodrome is specific for individual, patients which helps them to recognise the attack in time.

The second *aura phase* can only be observed in a smaller group of patients, in patients with aura (MWA). The aura phase is accompanied with focal neurological symptoms, such as visual (bright lines, zig-zag lines, points or scotoma), speech or sensory disturbance (Lauritzen, 1994; Viana et al., 2016). The symptoms last from a few minutes to an hour. In some cases, the aura phase is not followed by headache. Aura symptoms are noticed in 20% of all migraine cases.

The *headache* occurs in the third phase. The headache is characterized by an intense unilateral (rarely bilateral) pulsing, throbbing nature. The sidedness of the headache has not strict laterality, it could change to the other side of the head (Bes et al., 2013; Headache Classification Committee of the International Headache, 2013; Lipton et al., 2004). The headache is mostly accompanied by photo- or phonophobia, nausea and vomiting. The symptoms in some cases are accompanied by an exaggerated pain reaction to normal sensory stimuli, termed allodynia. One headache period could last from 24 to 72 h.

In the last phase (*postdrome*), after the headache, the patients become exhausted and sleepy. They may experience weakness, minor mood changes or cognitive difficulties. Generally, tiredness or depression characterize the last phase, however some patients feel themselves refreshed or even euphoric.

### **Pathology, pathomechanism**

The exact pathomechanism of migraine is not entirely understood yet. Previous studies hypothesised, that the abnormal function of the trigemino-vascular pathway has the key role in the migraine pathomechanism (Pietrobon and Moskowitz, 2013). The dural perivascular afferent fibres are part of the trigeminal nerve. The local nociceptive information is transmitted to the caudal trigeminal nucleus. During the dural afferent activation, local inflammatory activation starts, substance P and CGRP are released from the trigeminal afferent nerves. The transmitter release causes a local neurogenic inflammation. The nociceptive information is conducted through the periaqueductal grey mater, thalamus (ventral postero-medial nucleus (VPM) and posterior nucleus) to the cortex. From the VPM, the fibre bundles are mainly ending in the primary and secondary sensory cortex and in the insula. The bundles from the posterior nucleus end in other brain areas, such as visual, cingular or auditory cortex (Goadsby, 2009; Moskowitz, 1992).

The origin of the sensitisation of the dural afferent is not clearly understood. Previous animal experiments revealed that the local afferent nerves could be activated by inflammatory mediators, called “inflammatory soup”, (Bove and Moskowitz, 1997). During this activation local neuropeptide concentration increases (Levy, 2009) not only in the local dural area, but also in the jugular vein (Hoffmann et al., 2012).

Another key element in migraine pathomechanism is the cortical spreading depression (CSD). The CSD is a slow cortical depolarization wave on the surface of the brain lasting 1-2 minutes (Leao, 1947). As a consequence of the depolarisation, the local membrane potential changes, neurotransmitters are secreted, and a continuous hyperaemic wave starts to spread across the cortex. CSD was examined in ischaemia or brain injury (Bere et al., 2014; Pietrobon and Moskowitz, 2014), but also in normal brain. Trigeminal sensitisation can be induced by CSD (Hadjikhani et al., 2001), and local inflammation caused by the mediators (Levy, 2012). The

connection between CSD and migraine (dominantly MWA) seems to be proved, however the origin of the CSD is still not clear in patients with migraine (Charles and Baca, 2013). One possible explanation is the increased level of sensitivity of migraine patients' cortex (Afra et al., 2000b).

As it was shown above, the role of the neuropeptides could represent significant importance in trigeminal sensitisation and in pathomechanism of migraine. The most known neuropeptides, taking part in the migraine pathomechanism, are the CGRP, substance-P (SP) and VIP (Edvinsson, 1991; Edvinsson and Uddman, 2005).

The presence of CGRP is also notable in the trigeminal afferents, trigeminal ganglion and in the locus coeruleus (Shimizu et al., 2007; Tajti et al., 2001; Uddman et al., 2002). Migraine connected structures, such as periaqueductal gray matter (PAG) or raphe magnus, show increased VIP concentration (Tajti et al., 2001). It is important to note, that intravenous VIP, contrary to CGRP, does not induce migraine like headache (Hansen et al., 2006). In the last decades another peptide, the PACAP-38, showed important role in migraine pathomechanism. The influence of PACAP-38 is revealed in nociceptive processes and local dural vasodilatation in animal models (Gupta et al., 2010; Nemeth et al., 2006). PACAP-38 expression revealed in migraine-related brain areas, such as trigeminal ganglion, nucleus raphe magnus, locus coeruleus and PAG (Legradi et al., 1994; Tajti et al., 2001). The blood plasma concentration of PACAP-38 is lower in migraineurs compared to healthy individuals, however during headache, the concentration is increasing (Tuka et al., 2013). PACAP-38 infusion could cause also migraine-like headache (Schytz et al., 2009), furthermore, trigeminal ganglion stimulation can induce PACAP-38 secretion in the trigeminal ganglion and also in the blood serum (Tuka et al., 2012).

Genetic factors also play role in migraine pathomechanism. Clinical data and epidemiological studies suggest that first degree relatives have higher risk for migraine (Russell et al., 2002). Twin studies found almost 50 percentage risk for migraine coincidence (Honkasalo et al., 1995). In the past years genom wide analyses (GWA) identified 38 different locus that could connected to migraine. Familiar hemiplegic migraine is the most important from the monogenic forms. The autosome dominant disease, causing one sided motor symptoms. The heterogenic disease has three subtype (FHM1,2 and 3) connected to three difference genetic gene mutation:



CACNA1A, ATP1A2 and SCN1A respectively. Migraine with polygenic background has heterogeneous background. The gene alterations connected to neuronal and vascular functions. These genes related to glutamate metabolism, ion channels, ion metabolism nitricoxid pathways (Sutherland and Griffiths, 2017).

The patomechanism of MWA and migraine without aura (MWOA) subgroup may have a different background (Manzoni and Torelli, 2008; Ranson et al., 1991). It was suggested that the CSD is responsible for the aura symptoms (Hadjikhani et al., 2001; Petrusic and Zidverc-Trajkovic, 2014). Increased cortical hyperexcitability, as measured by visual evoked potentials and transcranial magnetic stimulation (TMS) studies (Connolly et al., 1982; Oelkers et al., 1999), was also mentioned as a potential trigger factor of migraine, predominantly for MWA (Coppola et al., 2015a; Sand et al., 2008). PET and fMRI studies also strengthen this theory (Boulloche et al., 2010; Nosedá and Burstein, 2013; Vincent et al., 2003).

### **Imaging markers of migraine**

Structural MRI studies showed, that migraine could influence grey and white matter integrity (Dai et al., 2015; Kim et al., 2008; Valfre et al., 2008). VBM studies revealed extensive grey matter volume reduction in the insula, premotor cortex, motor cortex and in the frontal regions. The former investigation found negative correlation between the volume and the headache duration (Dai et al., 2015; Kim et al., 2008). Chronic migraine patients revealed more extensive grey matter loss compared to healthy or to episodic migraine patients (Valfre et al., 2008). Female patients showed increased grey matter loss in the prefrontal cortex (Dai et al., 2015).

Only few studies investigated separately the structural parameters in the two sub-groups namely MWA and MWOA (Granziera et al., 2014; Granziera et al., 2013; Rocca et al., 2014). Up to now, white matter microstructural integrity showed no differences between the two sub-groups, or the studies did not separate the subgroups for investigation (Chong and Schwedt, 2015; Szabo et al., 2012). However, there are findings showing dissimilarities in the diffusion parameters between MWA and MWOA in the visual pathway (Granziera et al., 2006; Nikolett Szabó, 2018). Furthermore, in our recent work, we found extensive disintegration of the white matter in migraine patients with aura, but not in patients without aura (Nikolett Szabó, 2018).

Resting state fMRI studies revealed various connectivity changes in migraine. Some of the changes referred to increased (Tedeschi et al., 2016), in some comparisons revealed decreased functional connectivity (Tessitore et al., 2013; Xue et al., 2012). Several previous studies investigated activity changes in migraine and found altered activity in regions connected to pain processing (Mainero et al., 2011a; Schwedt et al., 2013; Yuan et al., 2013). Only a few of previous studies separated the two sub-groups and analysed the RSN separately.

MRI spectroscopy studies revealed higher glutamate/glutamine ratio and lower gamma butyric acid level in the occipital lobe of MWA patients. N-acetyl aspartate level was also increased (Bridge et al., 2015; Sarchielli et al., 2005), what suggest as possible hyperexcitability.

## **Therapy**

Besides possibly avoiding the triggering factors, the medical therapy of migraine includes acute headache therapy and interval drugs.

Acute therapy include several drugs for non-hospital use. Non-steroid painkillers are the first choice to eliminate headache. According to the recommendation of the American Headache Society (Marmura et al., 2015) diclofenac, aspirin and paracetamol proved to be mostly effective (Class I study) for the headache. Other painkillers such as ibuprofen or tramadol are could also be effective (Class II). Triptans (sumatriptan, zolmitriptan, frovatriptan) proved to be useful in acute migraine therapy (Class I). Other medications such as ergot alkaloids (Class I), octreotide (Class I) or even magnesium (Class II) could be useful in acute headache.

According to the guidelines of the American Headache Association, in the emergency management of migraine the intravenous metoclopramide, prochlorperazine and subcutaneous sumatriptan therapy should be the first choice. Intravenous acetaminophen, intravenous acetylsalicylic acid, parenteral chlorpromazine, intravenous dextropropofol, intravenous diclofenac, intravenous dipyron, parenteral droperidol, parenteral haloperidol, intravenous ketorolac, intravenous valproate may also be offered to adults with migraine attack (Marmura et al., 2015; Orr et al., 2016).

<b>Treatment</b>	<b>Efficacy</b>	<b>Adverse Events</b>
Acetaminophen 1 mg IV	Possibly effective	No serious or frequent Adverse Event
Acetylsalicylic acid 0.5–1.8mg IV	Likely effective	No serious or frequent adverse events. Better tolerated than sumatriptan
Chlorpromazine 0.1–25 mg IV	Possibly effective	Postural hypotension and drowsiness are common.
Dexamethasone 8–24 mg IV	Highly likely to be effective	Dizziness and brief burning pain more common in dexamethasone group.
Dexketoprofen 50 mg IV	Likely effective	No serious or frequent adverse events
Diclofenac 75 mg IM	Possibly effective	No serious or frequent adverse events
Dihydroergotamine 1 mg SC, IV	Possibly effective	In class 3 study, 305 adverse events among 152 patients randomized to DHE
Dipyrone 1 gm IV	Likely effective	No serious or frequent adverse events
Droperidol 2.5–8.25 mg IM	Likely effective	In class 2 study, akathisia (31%), asthenia (25%), somnolence (20%), and anxiety (16%) were common among those who received 2.75 mg dose
Haloperidol 5 mg IV	Likely effective	In class 1 study, no difference in adverse events vs metoclopramide. In class 3 study, 80% reported adverse events including
Ketorolac 30–60 mg IM, IV	Likely effective	Well tolerated
Metoclopramide 10–20 mg IV	Highly likely to be effective	Akathisia occurs in a minority of patients. No substantial differences vs active comparators
Prochlorperazine 10 mg IV	Highly likely to be effective	Akathisia and drowsiness were common
Sumatriptan 6 mg SC	Highly likely to be effective	In ED-based studies, adverse events in 50% of patients
Valproic Acid 500–1000 mg IV	Possibly effective	Minimal adverse events

*Table 3. Emergency Treatment of Migraine*

The European guideline for the headache management similar as the American guideline. However, there are some important differences. Steroids, valproate are possibly effective

according the American, but not included in the European. Opioids and haloperidol got also possibly effective evidence in the american guideline, but found ineffective in the european (Evers et al., 2009).

Beta-receptor blockers (propranolol or bisoprolol), antidepressants (amitriptylin), Ca<sup>++</sup> channel blockers (verapamil) or antiepileptic drugs (topiramate, valproate) are used for prophylactic therapy. In chronic form, the local injection of botulinum toxin proved to be an effective therapy (Evers et al., 2009; Matharu et al., 2017) (Table 4).

	name of drugs	dosage	level of evidence
suggested for first choice	metoprolol	50-200 mg	A
	propranolol	40-420 mg	A
	flunarizine	5-10 mg	A
	valproate	500-1800 mg	A
	topiramate	25-100 mg	A
suggested for second choice	amitriptylline	50-150 mg	B
	venlafaxin	75-150 mg	B
	naproxen	2x250-500 mg	B
	patesides	2x 75mg	B
	bisoprolol	5-10 mg	B
suggested for third choice	ASA	300 mg	C
	gabapentin	1200-1600 mg	C
	magnesium	24 mmol	C
	tanacetum	3-6,25 mg	C
	riboflavin	400 mg	C
	conevim Q10	300 mg	C
	candersartan	16 mg	C
	lisinopril	20 mg	C
	methysegride	4-12 mg	C

Table 4. Prophylactic therapy of migraine

## *Resting state fMRI*

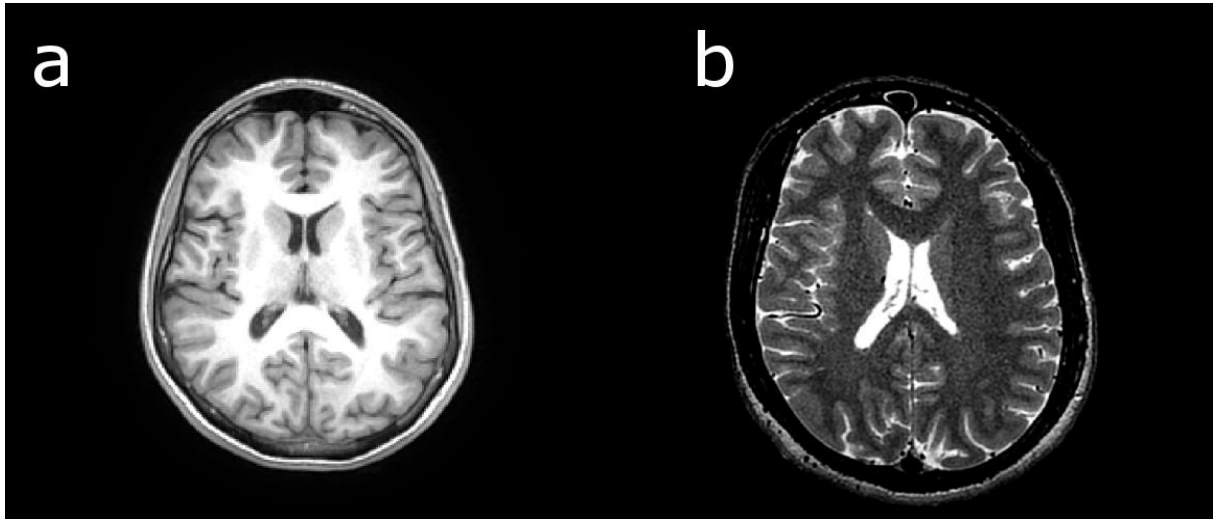
### **Basics of MRI**

The basics of MRI imaging are based on the impaired number of protons in molecules. The clinical or research MRI scanners use hydrogen ion (proton) as mediator. Because of the high density of hydrogen, we are able to measure notable signal. In normal circumstances, atoms are aligned randomly in space and rotate. This precession movement induces angular momentum. If the atom containing unpaired number of protons, will also has a magnetic momentum. The angular velocity of the precession is specific for the substance and only dependent on the magnetic field the substance experience. If we put this material (test structure, human body, etc.) into a high magnetic field, the spins of all molecules are regularized along the main magnetic field. This regularisation does not happen immediately, and the natural characteristics of the measurable material can also influence it. This phenomenon is called T1 relaxation (**Figure 1/a.**), and it describes the longitudinal magnetisation of the material. For example, the longitudinal magnetisation of the CSF is slow, but the T1 relaxation of white matter or the bones is faster, which makes it understandable how we can differentiate the various structures with the technique. In practice, we apply a transversal electromagnetic impulse to the material that flips the spins to the perpendicular plane and we are measuring the signal while the material is regaining to the longitudinal magnetisation.

Another MRI phenomenon is the T2 relaxation, what describes the transversal magnetisation. If we apply a 90-degree electromagnetic field, the spins move along with the transversal axis. In homogenous magnetic field the spins start a coherent precession, and a receiver coil in the transversal plane can measure a sinus wave. However, in the measured materials the local magnetic field is inhomogeneous, which is due to local molecular-molecular interactions, the local spin precession is gradually becoming incoherent, therefore the amplitude of the sinus signal is exponentially decreasing (**Figure 1/b.**).

T2\* is a special T2 imaging technique. In this case not only the molecular-molecular interactions influence the T2 relaxation, but there are more specific differences of the magnetic field. These differences can occur in areas, where the susceptibility is high. These areas are for

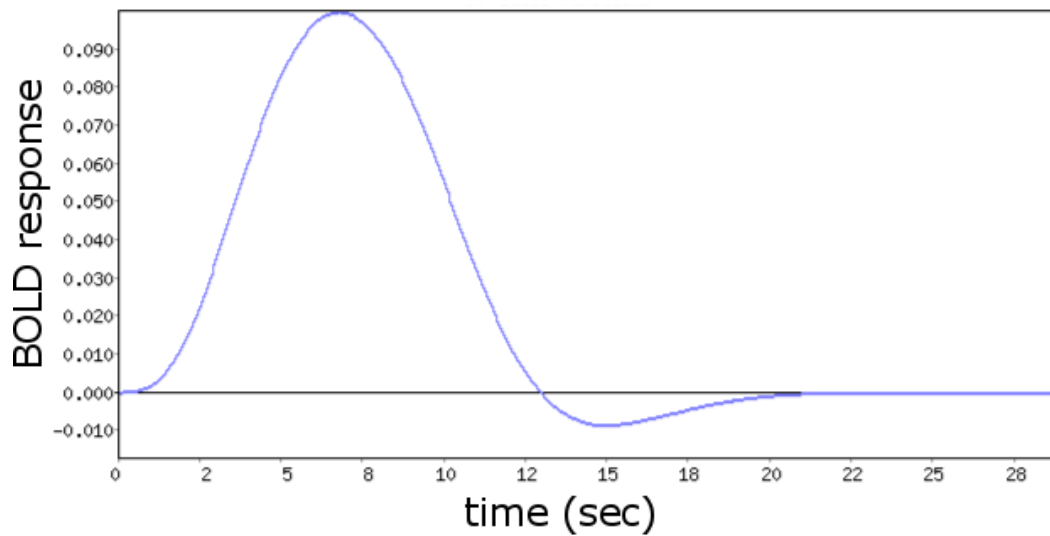
example the air-body border or around veins, or because of the paramagnetic nature of the deoxy-hemoglobin.



**Figure 1.** The representation of the T1 (a) and T2 (b) weighted images.

### Functional MRI

The fMRI is based on a T2\* EPI technique, where a special signal, as called blood oxygen level dependent (BOLD) signal is measured. The blood, more precisely, the deoxyhaemoglobin has a light paramagnetic nature, while oxyhemoglobin is diamagnetic (Ogawa et al., 1990). This changing paramagnetism due to the alteration of local deoxyhemoglobin concentration can be measured during fMRI scans. During a specified task (e.g.: finger tapping or visual checkerboard stimuli) the local neuronal activity increasing, the neurons' need for oxygen and nutrients are increasing. The local O<sub>2</sub> extraction is increasing, the deoxyhemoglobin concentration rising. After 3-6 s, the local cerebral blood flow becomes elevated, the deoxy hemoglobin is washed out, the oxy-deoxy hemoglobin ratio increasing. The EPI sequence measures this decreasing deoxy- (increased oxy-) hemoglobin phase. The connection between the increased metabolic demand and the vascular response causing the decrease of deoxyhemoglobin concentration is called hemodynamic response (**Figure 2.**). There is an important thing here to consider: The EPI sequence does not measure neuronal activity, but an indirect local hemodynamic response.



**Figure 2.** The schematic illustration of the hemodynamic response function

The paradigm could be block design, where the stimuli come repeatedly over a half a minute or so, or we could use single stimuli, as called event related fMRI. The main purpose of the task based fMRI is to separate the areas, where we can detect task dependent changes of the BOLD signal. The analysis in the first level locate the area of changes in each measured individual, dependent from the task.

The neuronal activity in task free state showed a natural fluctuation (Biswal et al., 1995; Raichle et al., 2001). This fluctuation is measurable by several neuroimaging methods (MEG, EEG). To analyse the whole brain resting state signal with MRI (fMRI) is an ideal method. In the scientific literature, there are two major approach for identifying resting state fMRI signal. The “seed-based” method investigate the relatedness of the activation in a particular region (region of interest – ROI) with the rest of the brain. The other approach is a various selection of model free analyses. These methods identify signal variation at a subject or group level that are not specified by a pre-existing hypothesis.

### **Resting state brain activity, resting state fMRI**

As it was mentioned above, the human brain does not rest in task free state, continuous neuronal activity can be measured. This neuronal activity shows fluctuation, the activity is not constant.

The first investigations used PET to measure the resting metabolism of the brain (Marchal et al., 1992; Pantano et al., 1984). Cortical metabolism was showed to be decreased with advancing age. White matter of basal ganglia was not affected by similar effect. The first investigations' with PET mostly concentrated to Alzheimer's disease and other dementias. These findings showed decreased metabolism in widespread regions of the cortex (Kumar et al., 1991). Later, another study demonstrated relatively high metabolism in healthy subjects in the posterior and anterior cingulate cortex, in task free state (Raichle et al., 2001). It is important to note, the decreased activity in these regions were strongly connected with the patients' neurophysiological tests and the cell loss via post-mortem investigations (Rapoport, 1991). Later on, these regions showing highest metabolism with PET were shown to have a synchronous activity fluctuation in fMRI studies (Savio et al., 2017).

The resting state fMRI, as mentioned, does not measure directly the local cortical metabolism, but the local hemodynamic change, in response to the local neuronal activity. This resting state BOLD response shows coherent fluctuation between regions of the brain, which have no strict anatomical connections. These coherent fluctuations give us an opportunity to investigate coherent activity, called functional connectivity, between remote brain areas (Beckmann et al., 2005; Greicius et al., 2004).

There are two commonly used approaches for resting state fMRI investigations: the seed based approach and the independent component analysis (ICA). As the traditional task-based fMRI, in the seed based method, correlation between the activity of a predefined area and the rest of the brain is calculated (Cordes et al., 2000; Di Martino et al., 2008). Choosing the seed region appropriately (the known hubs of RSNs) one can depict the RSN and measure the functional connectivity within it. The method is relatively easy to perform; however the analysis requires a strong hypothesis (the seed) for testing the predefined regions' functional connectivity.

The other commonly used approach, is the ICA (Beckmann and Smith, 2005). ICA is a trilinear factorisation of the fMRI data such as

$$X_{ij} = \sum_{r=1}^R a_{ir} b_{jr} + \varepsilon_{ijk} ,$$

where,  $x_{ij}$  denotes the fMRI data at voxel location of  $j$  at time point  $i$ .  $\mathbf{A}=[a_{ir}]$  and  $\mathbf{B}=[b_{jr}]$  are the spatial and temporal characteristics of the  $r$  components. The decomposition works in a way



that the spatial maps (the columns of  $\mathbf{B}$ ) are maximally non-Gaussians. With this method functionally connected areas are identified, as called RSNs (Beckmann et al., 2005; Mantini et al., 2007).

These RSNs are well known in the scientific literature. At rest, the posterior and anterior cingulate areas showed the highest metabolism, based on previous PET investigations (Raichle et al., 2001). Resting state function connectivity also showed the highest correlation between these areas (Greicius et al., 2003). With a special importance, the anterior and posterior cingulate regions and the bilateral parietal regions make up the so called *default mode network* (Greicius et al., 2003). There are other 8-12 known resting state networks based on the method or the selection (e.g. lateral and medial visual network, right and left attention network, cerebellar network, somatosensory network, salience network, dorsal attention network, etc.).

Several neurological and psychiatric disorders were investigated via resting state fMRI. Alzheimer dementia showed decreased metabolism, according to PET and SPECT (Johnson et al., 1998) findings, in areas, defined as default mode network. Resting state fMRI studies strengthened these results (Greicius et al., 2004), showing lower resting state BOLD fluctuation and metabolism in Alzheimer's disease. It is important to note that these findings were in strong correlation with the patient's neurophysiological test results. Parkinson's disease showed functional connectivity disruption in the putamen, thalamus, caudate nucleus and sensory-motor areas (Hacker et al., 2012; Wu et al., 2009), and disruption of functional connectivity of the default mode network was also reported (Tessitore et al., 2012). Investigations on epilepsy revealed wide spectrum of alterations of resting brain activity. Increased basal ganglia functional connectivity was revealed with other brain regions (Luo et al., 2012). The role of the default mode network in epilepsy is contradictory, some groups found increased (Wang et al., 2011), other revealed decreased (Zhang et al., 2011) functional connectivity.

### *Resting state activity in primary headache disorders*

Several studies investigated the activity of the resting state functional networks in migraine and found various alterations of networks that are implicated in pain processing (Hadjikhani et al., 2013; Hougaard et al., 2015a; Hougaard et al., 2015b; Mainero et al., 2011a; Niddam et al., 2015; Tedeschi et al., 2015; Tessitore et al., 2015; Tessitore et al., 2013; Xue et al., 2012; Yuan

et al., 2013). Remarkably some of the studies found increased, others decreased functional connectivity in migraine. Furthermore, while several studies investigated resting state functional networks in migraine (Tessitore et al., 2013; Xue et al., 2012), up to now there are only a few studies that investigated patients with MWA and MWoA separately (Hougaard et al., 2015b; Tedeschi et al., 2016).

In CH, former studies agreed on the altered functional connectivity of the hypothalamus (Qiu et al., 2015b; Qiu et al., 2013; Yang et al., 2014), and also on the alteration of the connectivity of other regions, part of the pain matrix, such as the medial frontal cortex and the cerebellum, sensorimotor network (Rocca et al., 2010).

One of the key features of migraine as well as of CH is the cortical hyperexcitability. In migraine, cortical hyperexcitability, as a potential trigger factor of migraine, is often mentioned (Afra et al., 2000b; Antal et al., 2005; Aurora et al., 1998). Importantly, cortical hyperexcitability is more robustly represented in MWA as demonstrated in visual evoked potential (VEP), TMS, PET and fMRI studies (Brigo et al., 2013; Coppola et al., 2015b; Cucchiara et al., 2015; Datta et al., 2013; Sand et al., 2008).

While the pathomechanism of the two primary headache disorders are distinctly different, there are common features of the diseases and also the pathomechanism. One of these is the increased cortical excitability which was also confirmed in CH (Chadaide et al., 2007; Cosentino et al., 2015) with TMS.

While there is no direct evidence up to date that resting state fMRI has a connection to cortical excitability, but it seems plausible that because of the tight interconnection between the BOLD signal and the underlying neural activity, one or another feature of resting fMRI is related to the excitability alterations measured by electrophysiological approaches.

Most of the resting state fMRI studies investigated the connectivity between various regions and therefore build on the coherent activity in spatially distributed networks. The variation in the frequency and the amplitude of the resting state BOLD signal is usually neglected. The BOLD resting state fluctuation is a low frequency fluctuation (Beckmann et al., 2005; Mantini et al., 2007). To filter out the non-neural noise from the raw BOLD time courses most of the studies apply filters (Jin et al., 2013; Schwedt et al., 2013; Xue et al., 2012). However, neural

signal could be detected also in the higher frequencies (Boyacioglu et al., 2013b). Furthermore, a few recent studies started to analyse the amplitude of the low frequency fluctuation of the resting state signals (Kim et al., 2013; Zou et al., 2008) offering a unique insight into the resting brain activity in various diseases but not in migraine. The frequency and the amplitude changes of the activity of key pain processing regions is even more important in disorders such as migraine and CH, in which cortical hyperexcitability was reported.

## Objectives

The aim of our investigations was to seek functional changes in resting state fMRI networks with specific attention to the amplitude of the resting state activity in various frequency bands in primary headache disorders. The investigation has not just focused on the functional connectivity changes, but also the amplitude of the fluctuation. Our investigations assessed on alterations in pain-free period. Furthermore, correlation of the observed fMRI changes to clinical data, such as disease duration or cumulative headache days, were also tested.

## Methods

### *Participants*

Seventeen episodic CH patients and fifty-one episodic migraine patient were recruited from the Headache Outpatients Clinic of the Department of Neurology, University of Szeged and Semmelweis University. The diagnosis was based on the diagnosis criteria of the International Headache Society (Bes et al., 2013). The diagnosis was set up by experienced headache specialists. The recruited patients had no history of other neurological or psychiatric disorders. All patients were diagnosed with episodic headache and were scanned during an interictal phase.

All patient underwent clinical interview, which considered the disease duration, intensity of pain, average attack number per year and the sidedness of headache. Allodynia score and estimated lifetime attack number were calculated for all patients. Additionally, from migraine patients the type of headache (MWA, MWoA) was also acquired. The detailed demographic data are depicted in *Table 5* and *Table 6*.

	Healthy	Patients	p
N	26	17	-
gender (male)	23	15	n.s.
age (years; mean and SD)	37.92 (11.55)	37,82 (11.57)	n.s.
handedness (right)	26	17	n.s.
headache side (right)	NA	7	-
cumulative headache days (mean and SD)	NA	319.19 (243.3)	-

*Table 5.* Demographic data of the cluster headache and the control group.

	Migraine with aura	Migraine without aura	Healthy	p
N	18	33	32	-
age (years; mean and SD)	32.1 (8)	35.6 (8.9)	35.2 (11)	n.s.
gender (male)	3	3	2	n.s.
Allodynia (mean and SD)	1.6 (1.7)	3.2 (3)	NA	<0.05
Disease duration (years; mean and SD)	14.2 (8.6)	13.7 (9.1)	NA	n.s.
ATK/life (days; mean)	461 (615)	656 (626)	NA	n.s.
VAS (mean and SD)	7.6 (1.3)	8.7 (1.2)	NA	n.s.
ATK/years (days; mean and SD)	29 (26)	55 (45.6)	NA	<0.05

*Table 6.* Demographic data of the migraine and the control group

As control group twenty-six age and gender matched right handed participants were recruited for comparison to CH patients. For the MWA and MWoA groups, thirty-two healthy volunteers were recruited as controls. The controls had no previous history of any neurological or psychiatric disorders. The healthy volunteers also underwent detailed interview.

The study was approved by the ethic committee of the University of Szeged. All participants gave written informed consent to the investigation. The written consent and the study protocol were set in concordance with the Declaration of Helsinki (authority number: 56/2011).

### *Image acquisition*

The MRI imaging was performed on a 1.5 T GE Signa Excite HDxt scanner (Milwaukee, WI, USA). During the scan, head motion was restricted with foam padding around the head and the noise of the scanner was attenuated with earplugs. Subjects were asked to stay awake during the acquisition. For every participants' high resolution T1 weighed images (3D IR-FSPGR: TR/TE/TI: 10.3/4.2/450 ms; flip angle: 15; ASSET: 2, FOC: 25 x 25 cm; matrix: 256 x 256; slice thickness: 1 mm) and resting state fMRI protocol with echo planar imaging technique (TE:

40ms; TR: 3000 ms; matrix 64 x 64; FOV: 30 x 30 cm; slice thickness: 6 mm; flip angle:90; NEX: 1; ASSET: 2.0 Ph; Phase per Loc: 128; volumes: 200) were acquired.

### *Image analysis*

All image processing were performed by FMRIB's Software Library (<http://www.fmrib.co.uk/fsl>; Oxford; UK) toolkit.

### **Data preprocessing**

Non brain tissues were removed from all T1 high resolution images using the brain extraction tool (BET) (Smith, 2002). The brain extracted structural images were registered to standard space brain image (MNI152 T1 image; 2mm slice thickness) with linear (12 DOF; FLIRT) and the with non-linear (FNIRT) registration for each participant (Jenkinson et al., 2002). The result of the brain extraction and registration was checked manually and the brain extraction mistakes and misregistartion were corrected manually.

The preprocessing steps of the fMRI data were carried out by FEAT. The first two non steady state images were wiped out for all 4D fMRI images. The non-brain tissues were removed usingn BET. The images were motion corrected by MCFLIRT (Jenkinson et al., 2002) to the middle functional image and spatially smoothed with Gaussian kernel of 6 m FWHM. A high pass filter with 100 s cutoff was also applied to all functional images. Because in the further analysis we were to investigate the higher frequencies, low pass filter was not applied. All preprocessed images were registered to their own T1 structural images with linear registration (FLIRT) with 6 DOF. The functional images were registered to a standard image (MNI152 T1 image, 2mm isovoxel size) using the matrices and warp-fields previously generated. In the last step all standard space registered images were resampled to 4mm isovoxel to ease the computational burden.

Additionally, in CH patients, because the headache is strictly unilateral, according to the previous studies, we normalized the data to the headache side creating three subgroups. (1) The patients, who had headache in the left side, were inverted along the midsaggital axis using fslswapdim command. With this method, we created a group that have only headache in the right side. The side inversion was applied on the high resolution T1 images and also on the

resting state images. (2) We repeated this method on the other sided (right headache sided) images, created a left headache sided group. (3) As a third group non-inverted dataset was also analysed.

### **Independent component analysis**

Large scale neuronal RSN were identified by independent component analysis using MELODIC. The group specific networks were identified using multi session temporal concatenation approach (Beckmann et al., 2005; Mantini et al., 2007).

The preprocessed functional data were voxel-wise de-meaned, variance normalized, then voxel wise temporal concatenation was applied. The resulted 4D data were decomposed into set of independent components that characterized the underlying processes in the spatial and temporal domains in such, that the spatial maps get maximal non-Gaussian. The number of components was automatically estimated by applying the Laplace approximation to the Bayesian evidence of the probabilistic principal component model (Beckmann and Smith, 2005). The spatial maps were thresholded to  $p < 0.5$  variance under the Gaussian-Gamma mixture model (Woolrich et al., 2005)

Spatio-temporal components representing artefacts, outliers, non-pain related networks were excluded from further analysis. The network identification and exclusion was based on previous studies. Based on these articles, the selected eight networks for further analysis were (Qiu et al., 2015a; Qiu et al., 2013; Yang et al., 2013): default mode network, right attention network, left attention network, medial visual network, lateral visual network, cerebellar network, somatosensory network and salience network.

### **Frequency specific amplitude of the resting state activity**

The frequency specific modulation of the amplitude of resting state activity and the frequency specific connectivity were analysed by discrete wavelet decomposition (Wavelet Toolbox of the Matlab software package).

The discrete wavelet decomposition is an implementation of the wavelet transform using a set of predefined wavelets. Wavelets are brief waves, they are infinitely extended and their oscillations decay to zero rapidly, satisfying the admissibility condition:

$$\int \Psi(t) dt = 0.$$

The wavelet can scale, decompose and translate a signal into mutually orthogonal set of wavelets. By dilating and translating a “mother” wavelet ( $\Psi$ ) and a “father” wavelet ( $\Phi$ ).

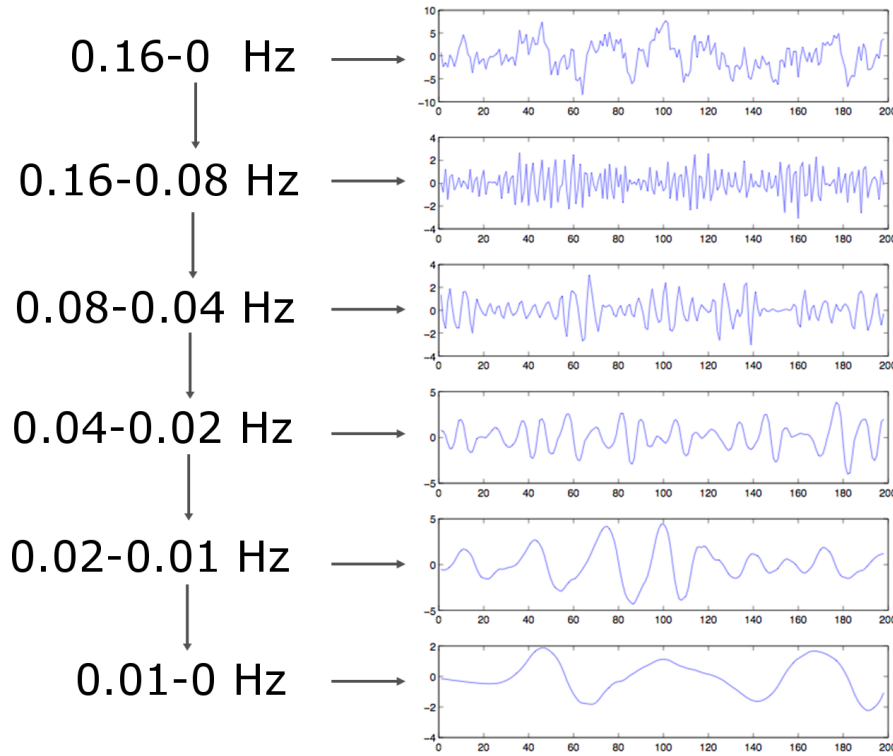
( $\int \Phi(t) dt = 1$ ) a wavelet family can be obtained:

$$\Psi_{jk}(t) = \frac{1}{\sqrt{2^j}} \Psi\left(\frac{t - 2^j k}{2^j}\right);$$

$$\Phi_{jk}(t) = \frac{1}{\sqrt{2^j}} \Phi\left(\frac{t - 2^j k}{2^j}\right);$$

where  $j$  is index of the scale  $S_j = 2^j$  and  $k$  indexes the  $K = n/2^j$  location in time. The Daubechies wavelet was used in our analyses as mother wavelet. The analysis by using a halfband filtering, decomposes the data over a hierarchy of scales ( $S_j$ ). At each scale the data is split into two orthogonal components: details ( $d_{jk}$ ) containing the high frequency information and approximations ( $a_{jk}$ ) containing the low frequency information (**Figure 3**). By this method the network's time courses were divided into five consecutive frequency bands (band1: 0.16-0.08 Hz; band2: 0.08-0.04 Hz, band3: 0.04-0.02 Hz; band4: 0.02-0.01 Hz; band5: 0.01-0 Hz).





**Figure 3.** Schematic graphic representation of the wavelet halfband filtering

The frequency specific connectivity was compared with a modified dual regression approach (see below).

To measure the mean amplitude of the resting state activity in the various frequency bands, an envelope was fitted to the absolute maximum values of each frequency band. The minimum of the following function was identified:

$$f(t) = \frac{d \left( \text{sgn} \left( \frac{dy}{dt} \right) \right)}{dt} .$$

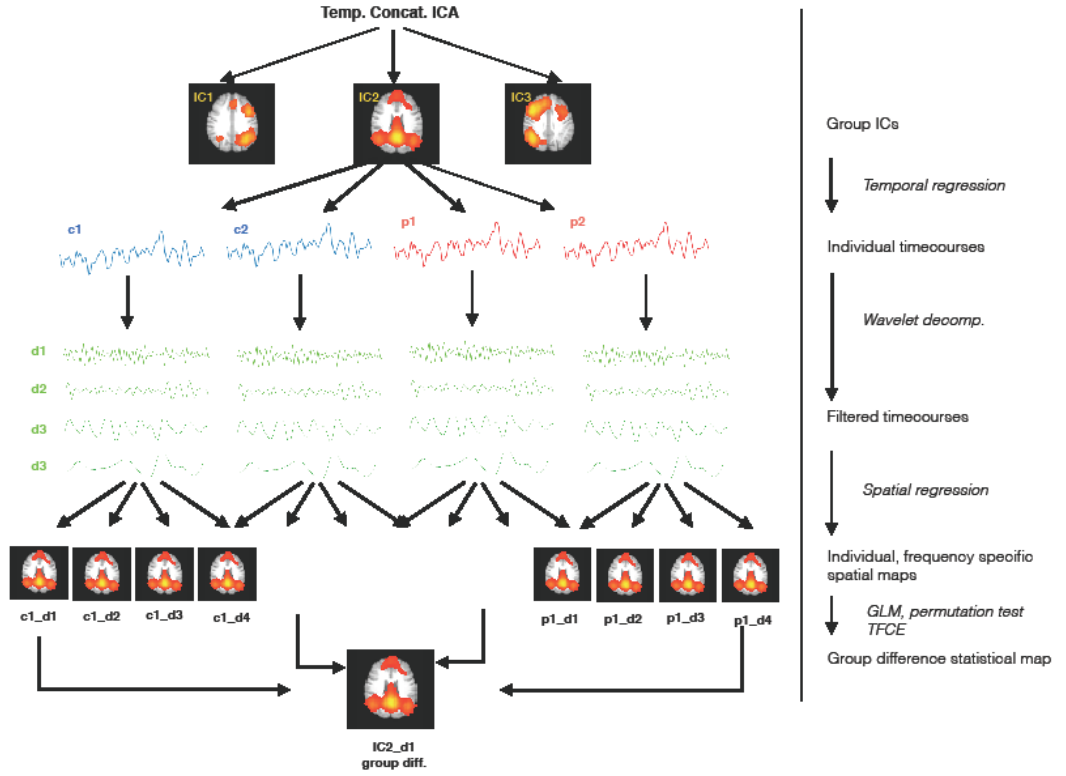
A linear interpolation of these points were used to create an envelope. The envelopes are averaged over time for each network to describe the mean activity of a given RSN in a specific frequency band.

Furthermore, not just the networks mean fluctuation went under frequency decomposition and envelope fitting, but also the voxel-wise preprocessed data for each participant. The voxel-wise decomposition and envelop fitting were performed by a house-made Matlab script.

After each processing step visual check was performed.

### **Differences between groups of the resting state data**

The RSNs' connectivity were compared by a modified dual regression approach. The previously defined networks' spatial maps were regressed into all individuals' functional images to obtain individual specific time courses for each network. In the second step the individual network time courses were regressed to the functional image, to get individual-specific network distribution. In addition, using the wavelet decomposition mentioned above, in the second step we used the frequency-specific time courses for the second regression to get frequency specific network distribution for each individual. The modified dual regression scheme depicted in **Figure 4**.



**Figure 4.** Schematic representation of the modified dual regression method

The frequency specific networks' comparison was accomplished across groups using a permutation based cluster analysis (5000 permutation) (Nichols and Holmes, 2002). The modelling was accomplished using standard General Linear Model (GLM). The design encoded for group membership. The design also included age and gender as covariance. For statistical analysis, threshold-free cluster enhancement was used (TFCE) and corrected for multiple comparisons, family wise error (FWE), across space within each permutation network (Smith and Nichols, 2009).

Similarly, a GLM-based permutation test was used to investigate the differences of the amplitude of the mean network time courses across groups in the individual frequency bands.

### **Connection between resting state activity and clinical data**

The cumulative headache days and the disease duration, and the degree of networks' coactivation were also calculated. The correlations accomplished in the General Linear Model framework were calculated with permutation based test for each voxel (5000 permutation) and corrected for multiple comparisons (FWE).

### **Mean amplitude of the resting state networks**

The average time courses of each network were calculated by wavelet decomposition and envelop fitting. The time course data were compared with two sample T-test between groups.

## Results

### *Demographic data*

The age and clinical data, as disease duration, attack number or allodynia scores were compared by two-sample T-test. The gender differences were compared by chi square test. There were no significant differences between any groups' age and gender distribution in any comparisons. Furthermore, there was no significant difference between MWA and MWoA groups' disease duration. There was a difference between the two subgroups' allodynia score, the allodynia score was higher in the MWoA group ( $p < 0.05$ ).

### *Resting state fMRI alterations in cluster headache*

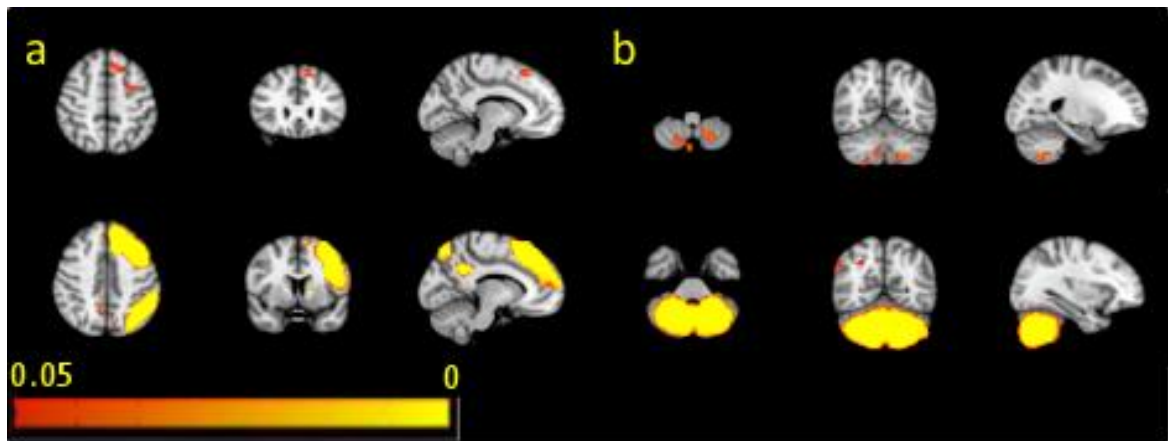
The MELODIC analysis found different number of components in all three investigated CH datasets (plus healthy controls). In the case of the left sided dataset 29 independent components were found. The right sided and the original datasets revealed 30 independent components. All of the three investigated groups' analysis revealed all eight investigated networks, mentioned above.

### **Frequency specific expression of the resting state networks**

#### *Left sided dataset*

The modified dual regression approach revealed alterations of the left attention network in two frequency bands: 0.08-0.04, 0.04-0.02 Hz. The increased coactivation was measured ipsilateral to the headache side. Increased coactivation was found in CH group compared to controls. The alterations were localised within the left superior frontal gyrus and in the left medial frontal cortex ( $p < 0.03$ , **Figure 5/a**)

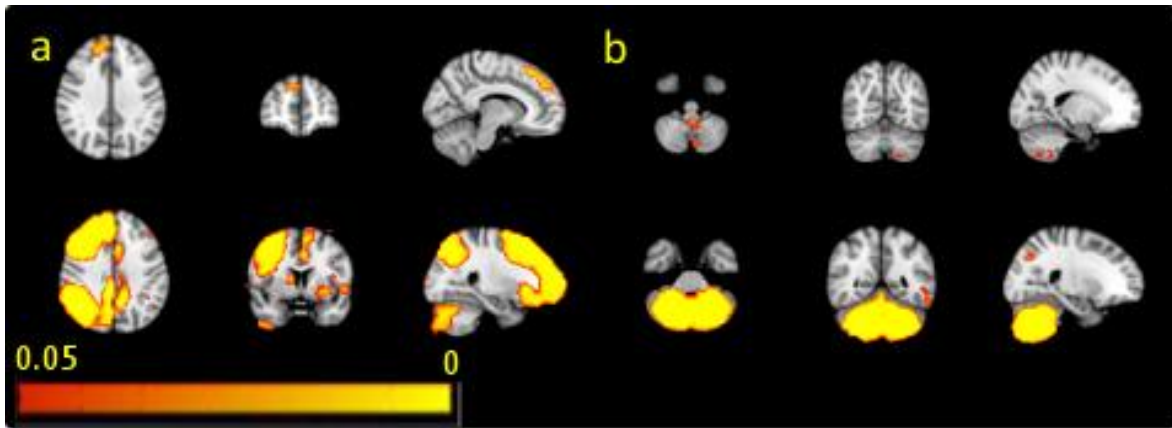
Significant increased coactivation was found in CH within the cerebellar network in the 0.02-0.01 Hz frequency band, localized in both cerebellar tonsils ( $p < 0.03$ ; **Figure 5/b**). There were no other significant results in any RSNs, in any frequency band.



**Figure 5.** Altered activity in the left mirrored dataset. The left attention network showed increased activity in the ipsilateral superior frontal gyrus and in the ipsilateral medio-frontal cortex (a). The increased activity was measured at the frequency band 0.08–0.04 Hz ( $p < 0.05$ ). In the cerebellar network increased activity was found in the cerebellar tonsils at the frequency band 0.02–0.01 Hz ( $p < 0.05$ ) (b).

#### *Right sided dataset*

Increased coactivation within the right attention network was found in CH compared to controls in the 0.08–0.04 Hz frequency band. The results were found also ipsilateral to the headache side. The alteration localised in the right superior frontal gyrus ( $p < 0.003$ ) and in the right medial frontal gyrus ( $p < 0.05$ ; **Figure 6/a**). In the cerebellar network, increased coactivation was found in CH group in the 0.02–0.01 Hz frequency band, localised in the cerebellar tonsils ( $p < 0.05$ ; **Figure 6/b**). There were no other differences between any other RSNs in any frequency bands.

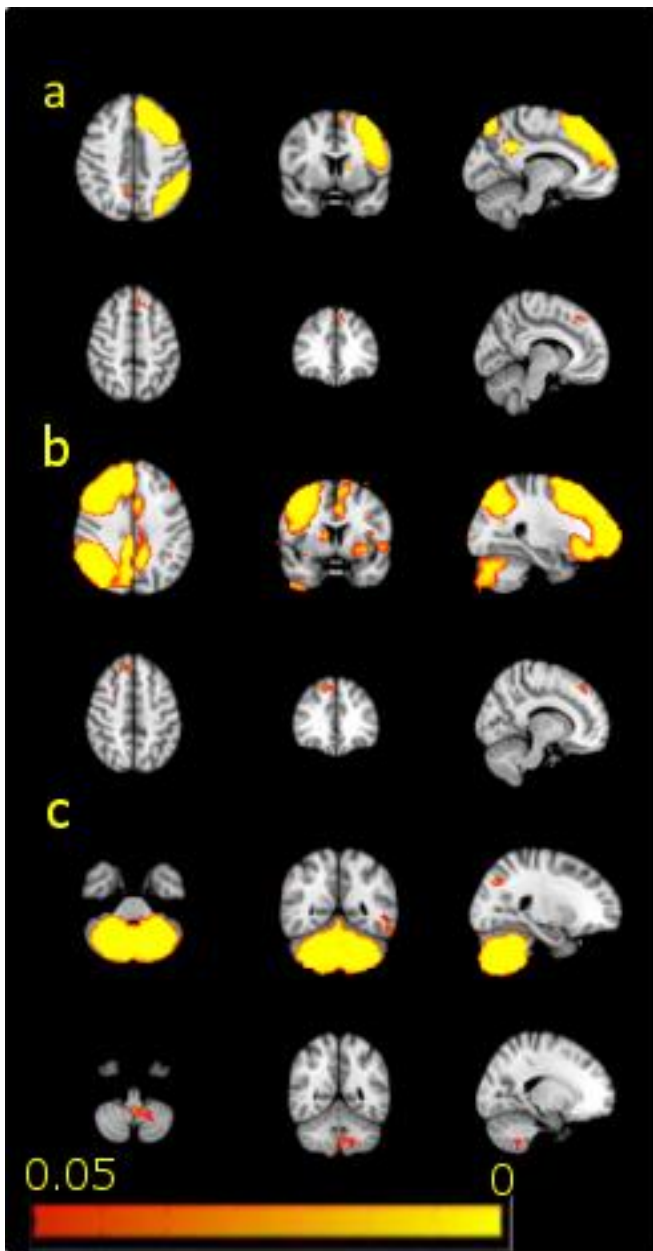


**Figure 6.** Altered activity in the right mirrored dataset. The right attention network showed increased activity in the 0.08–0.04 Hz frequency band ( $p < 0.01$ ) in the superior and medial frontal cortex (a). The analysis revealed decreased activity in the cerebellar network in the cerebellar tonsils (b) at the frequency band 0.02–0.01 Hz ( $p < 0.05$ ).

*Non-flipped, original dataset*

Increased coactivation was found in the left and the right attention network in the 0.08–0.04 Hz frequency band. The left attention network showed differences in the left superior frontal gyrus ( $p < 0.05$ ; **Figure 7/a**). The right attention network showed increased coactivation in the right superior frontal gyrus ( $p < 0.05$ ; **Figure 7/b**). The cerebellar network revealed increased connectivity in the inferior cerebellar vermis and in the left cerebellar tonsil (**Figure 7/c**). In all case the CH group showed greater coactivation.

There were no other differences between any RSNs in any frequency band in any dataset. The local maxima of the result were depicted in *Table 7*.



**Figure 7.** Altered activity of the original dataset. The left attention network showed increased connectivity in the left superior frontal gyrus (a;  $p < 0.05$ ). The right attention network revealed increased connectivity in the right superior frontal gyrus (b;  $p < 0.05$ ). Both attention network showed differences in the 0.08-0.04 Hz frequency band. The cerebellar network, at the 0.02-0.01 Hz frequency band, showed greater coactivation in the left cerebellar tonsil and in the vermis (c;  $p < 0.05$ ). The colour bar represents the threshold level. All images are overlaid on the standard MNI152\_2mm brain image.



	x	y	Z
Left flipped dataset			
Left attention network	50	76	64
Cerebellar network	56	33	9
Right flipped dataset			
Right attention network	40	88	53
Cerebellar network	54	31	11
Original dataset			
Right attention network	48	81	59
Left attention network	38	80	61
Cerebellar network	46	40	14

*Table 7.* The MNI coordinates of the local maxima of the increased coactivation in cluster headache patients.

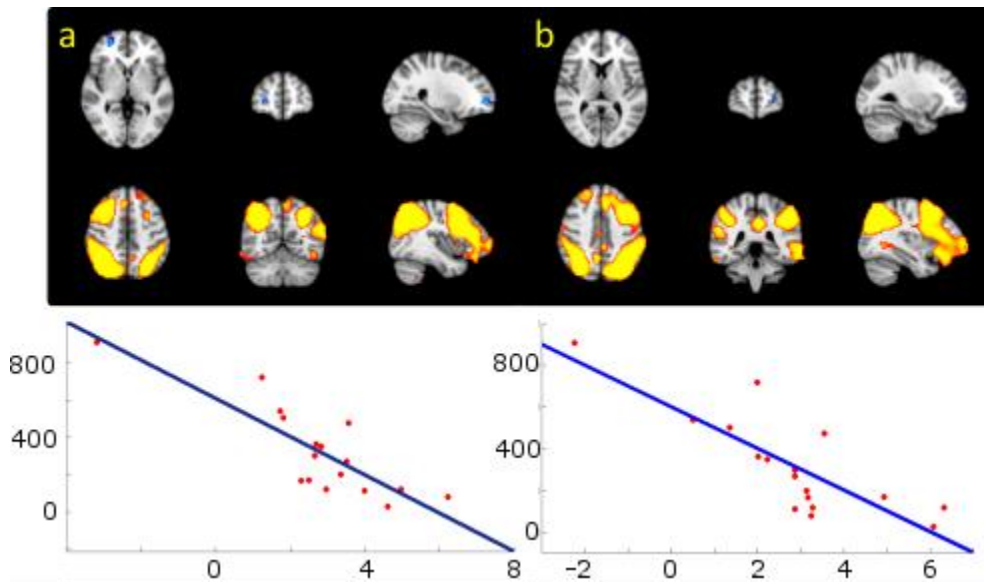
#### *Connection between resting state network and clinical data*

Correlation analysis between cumulative headache days and resting state functional connectivity revealed correlations in the left and in the right sided dataset.

The left sided dataset revealed negative correlations in the contralateral (right) attention network in the 0.08-0.04 Hz band, localized in the right frontal pole ( $p < 0.001$ , **Figure 8/a**).

The right sided dataset revealed negative correlation between the coactivation and the contralateral (left) attention network ( $p < 0.05$ ; **Figure 8/b**). The area of correlation localized in the 0.16-0.08 Hz frequency band, in the contralateral frontal pole.

There were no other correlations between any clinical data and resting state networks' functional connectivity in any frequency band.



**Figure 8.** Correlation was found between cumulative headache days and expression of the resting state activity fluctuations. In the left mirrored dataset, the contralateral attention network showed correlation with the cumulative headache days in the contralateral frontal pole ( $p < 0.05$ ) (a). The right mirrored dataset showed correlation in the contralateral attention network (b) near the ipsilateral frontal pole ( $p < 0.05$ ). The changes were depicted blue to light-blue. In the diagrams X axis represents the summed number of headache days. Y axis represents the mean Z-score of the two resting state networks.

### *Resting state fMRI alterations in Migraine*

The MELODIC analysis found 33 independent components in the healthy controls. Components representing artefacts were rejected and finally five networks went under further analysis: default mode network, right attention network, left attention network, medial visual network and lateral visual network.

## Alterations in the amplitude of the resting state networks

### *MWA vs. healthy controls*

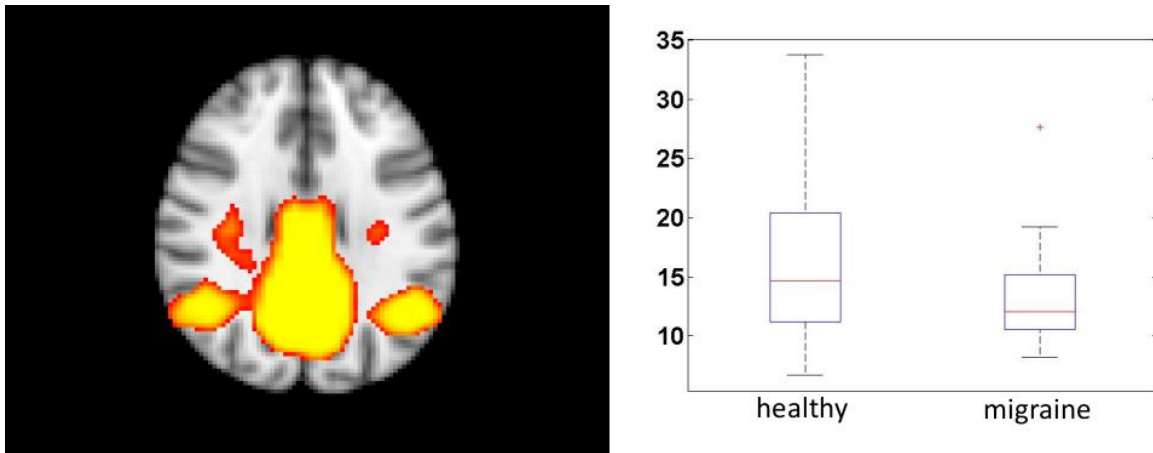
Our analysis showed that in the highest frequencies, (0.16-0.08 Hz) the amplitude of the resting activity was tendentially higher in the left attention network ( $p < 0.051$ ) and tendentially in the right attention network ( $p < 0.058$ ) in MWA as compared to healthy controls. There were no other significant results in any other frequency bands or in case of the non-filtered data.

### *MWoA vs. healthy controls*

The amplitude of fluctuation in the 0.08-0.04 Hz band was decreased in the MWoA group in the default mode network ( $p < 0.05$ ; **Figure 9**). There were no other differences between MWoA and healthy group in any other frequency band or in the non-filtered data.

### *MWA vs. MWoA*

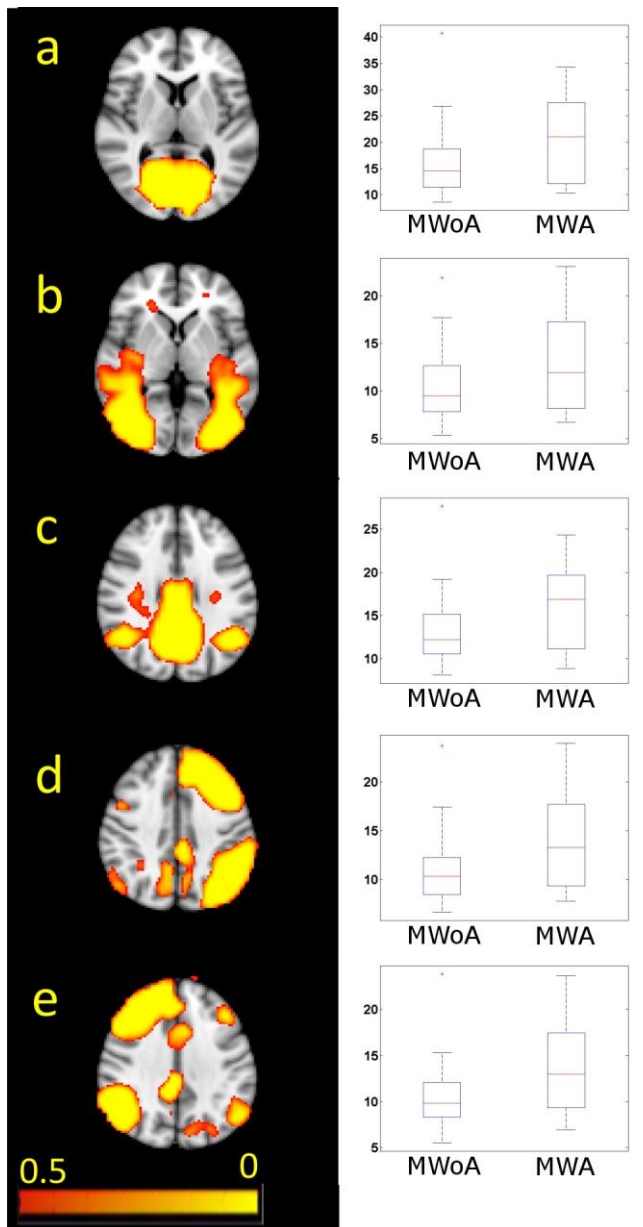
The amplitude of the fluctuation was higher in all investigated network in the 0.08-0.04 Hz frequency band ( $p < 0.05$ ) in the MWA group. Furthermore, the lateral visual network showed higher amplitude in the 0.16-0.08 Hz frequency band in the MWA group ( $p < 0.05$ ; **Figure 10**). There were no other differences in any other frequency band, neither in the non-decomposed data.



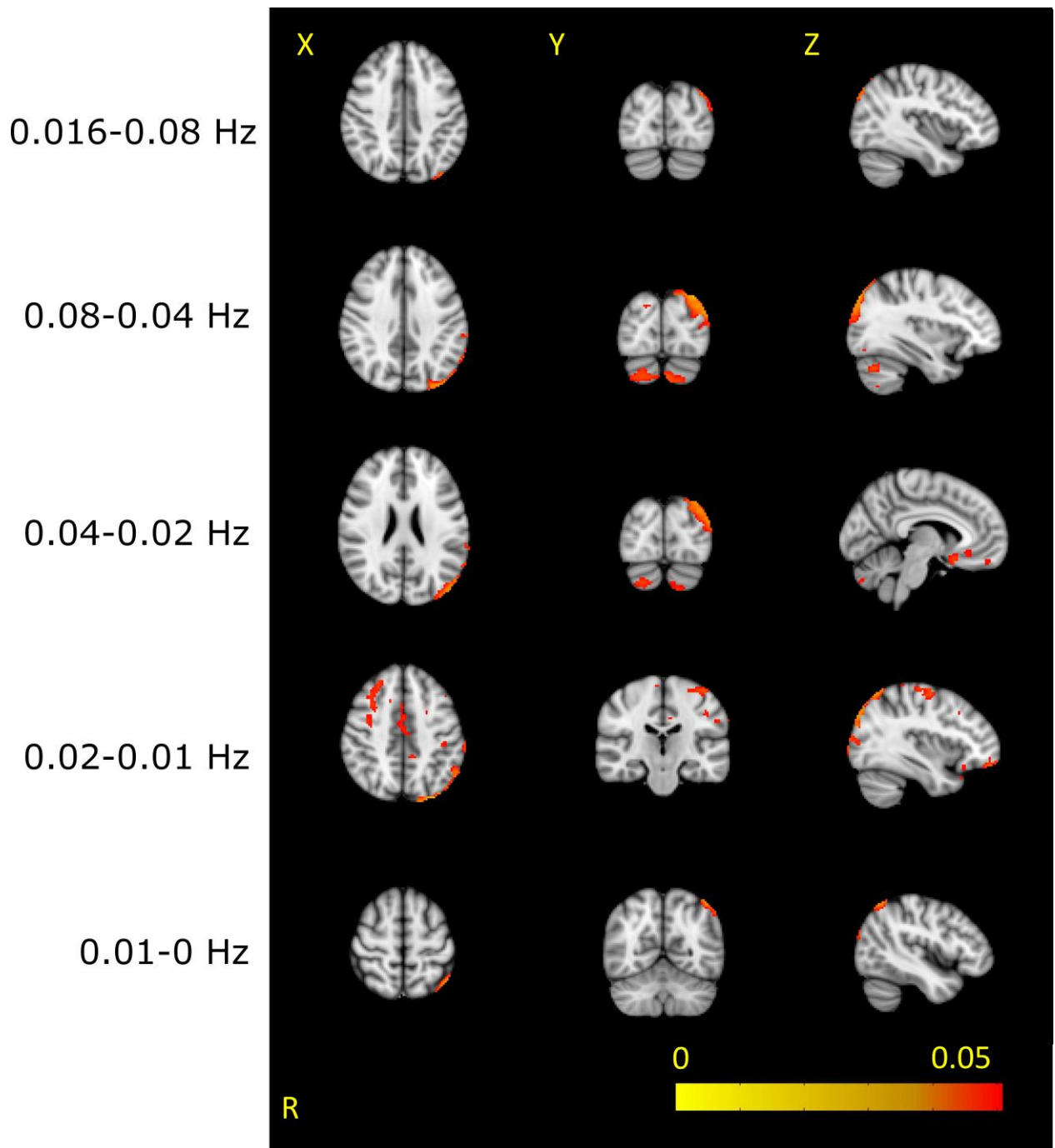
**Figure 9.** The default mode network showed higher amplitude in the 0.04-0.02 Hz in healthy group compared to migraine without aura. The images on the left depicting the resting state networks are thresholded at  $p < 0.5$  and overlaid on the standard MNI\_152 brain. The boxplots depicts the amplitude of the activity of the networks (arb. unit). The central mark is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extend to the most extreme data points.

#### *Voxel-wise comparison of the amplitude of resting activity*

The voxel wise comparisons of the amplitude of the resting state activity revealed higher amplitudes ( $p < 0.05$ ) in several frequency bands. The left parietal lobule showed higher amplitude in MWA in all frequency bands. Furthermore, in 0.08-0.04 Hz band higher amplitude was found in the both cerebellar hemispheres, left occipital junction and in the left occipital pole. In 0.04-0.02 Hz band, higher amplitudes were found in the cerebellum and in the anterior cingulate gyrus. In the 0.02-0.0 Hz band, MWA showed higher amplitude in the cerebellum, occipital pole, frontal pole, precentral gyrus and near the superior frontal sulcus (**Figure 11**). The detailed local maxima depicted in *Table 8*.



**Figure 10.** All of the investigated network ((a) medial visual, (b) lateral visual, (c) default mode, (d) left attention, (e) right attention) showed higher amplitude in the 0.08–0.04 Hz frequency range in migraine with aura compared to migraine without aura. The images on the left depicting the resting state networks are thresholded at  $p < 0.5$  and overlaid on the standard MNI\_152 brain. The boxplots depicting the amplitude of the activity of the networks in the 0.08–0.04 Hz frequency range (arb. unit). The central mark is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extend to the most extreme data points.



**Figure 11.** The frequency specific voxel wise comparison of the amplitude of the resting activity showed higher amplitudes in migraine with aura as compared to migraine without aura. The images are thresholded at  $p < 0.05$  corrected for multiple comparisons and overlaid on the standard MNI152\_2mm brain. The colour bar represent the significance level of the results.

	Region	side	x	y	z	p<	Z score	% diff
<b>0.016-0.08 Hz</b>	Inferior parietal lobule	L	-38	-82	40	0,03	-2,9	133%
<b>0.08-0.04 Hz</b>	Inferior parietal lobule	L	-34	-84	42	0,02	-3	173%
	Cerebellum	L	-6	-84	-40	0,04	-2,8	145%
	Occipito-temporal junction	L	-58	-70	0	0,03	-2,7	121%
	Occipital pole	L	-16	-96	14	0,05	-2,3	141%
	Inferior parietal lobule	R	14	-34	34	0,05	-2,5	135%
	Cerebellum	R	36	-34	-52	0,05	-2,7	137%
<b>0.04-0.02 Hz</b>	Cingulate gyrus	L	-6	14	-18	0,04	-2,5	159%
	Inferior parietal lobule	L	-34	-84	42	0,03	-3,1	196%
	Cerebellum	R	24	-84	-40	0,04	-2,6	178%
	Cerebellum	L	-14	-80	-46	0,05	-2,5	144%
<b>0.02-0.01 Hz</b>	Inferior parietal lobule	L	-34	-84	42	0,02	-3,2	199%
	Superior frontal sulcus	R	26	34	44	0,04	-2,6	120%
	Precentral gyrus	L	-44	-12	62	0,04	-2,8	167%
	Frontal pole	L	-34	52	-16	0,03	-2,9	195%
	Cingulate gyrus	L	0	-2	42	0,05	-2,5	118%
	Occipital lobe	L	-22	-92	12	0,04	-2,6	160%
<b>0.01-0 Hz</b>	Inferior parietal lobule	L	-44	-60	58	0,03	-3	163%

*Table 8.* Increased amplitude of resting state activity fluctuations in MWA as compared to MWoA. The coordinates represent the localisation of the maximal differences in MNI152\_2m standard space. Z-scores and percentile differences between the groups also depicted.

## Discussion

In this thesis we presented resting state functional MRI alterations in CH and migraine with novel analysis approaches. (I) Our first study revealed increased frequency specific resting state activity in CH patients in the attention network ipsilateral to the headache side and in the cerebellar network bilaterally. (II) Our second analysis showed that in migraine the amplitude of the activity of the RSNs in the 0.08-0.04 Hz frequency range was higher in MWA than in MWOA in all examined RSNs. On the contrary, in MWOA the amplitude of the activity fluctuation of the default-mode network was lower than in healthy controls. Furthermore, the amplitude of resting state BOLD fluctuation was higher in MWA in the highr frequencies in the medial frontal, anterior cingulate cortex and in the superior parietal lobule compared to MWOA even if RSNs were not considered. This increased activity must be understood as increased frequency specific coherent activity within networks and also increased amplitude of the BOLD fluctuation.

Several studies implicated cortical hyperexcitability in migraine patients (Antal et al., 2005; Gawel et al., 1983; Pierelli et al., 2013). Evoked potential studies showed higher amplitude of visual evoked potentials in migraine patients (Connolly et al., 1982; Oelkers et al., 1999). TMS study also found lower phosphene threshold in migraine (Aurora et al., 1998). Previous PET and fMRI studies showed higher activation in migraine to visual stimuli (Bouloche et al., 2010; Vincent et al., 2003).

The above mentioned studies showed us important results about the pathomechanism of migraine, however, they failed to separate the MWOA and MWA in their analysis. Interestingly, VEP studies revealed higher amplitude in MWA (Coppola et al., 2015a; Cucchiara et al., 2015; Sand et al., 2008). A TMS meta-analysis pointed out that the cortical hyperexcitability mostly true for patients' with aura, but not for MWOA (Brigo et al., 2013). The increased BOLD for photic stimuli were higher in MWA compared to MWOA (Cucchiara et al., 2015; Datta et al., 2013).

In CH the primary role of the cortical dysfunction was strengthened by former electrophysiological studies (Casale et al., 2008; van Vliet et al., 2003). A former TMS



stimulation study found hyperexcitability in CH patients similar to that in migraine (Cosentino et al., 2015). Interestingly, they found increased excitability ipsilateral to the headache side, which is in agreement with our findings of ipsilateral resting state activity alterations.

One possibility to explain our results is that higher cortical excitability (easier to evoke response from the cortex) could be paralleled with higher spiking activity of the cortex as shown by direct current stimulation studies (Antal et al., 2003; Bindman et al., 1964), which because of the higher energy demand would result in higher amplitude of BOLD fluctuation. Importantly, while it is tempting to propose that the cortical hyperexcitability and the higher amplitude of resting state activation is related, alternative explanations should not be dismissed.

It has to be noted that cortical hyperexcitability is not unanimously reported in migraine even with aura. In a TMS study the prevalence of stimulation-induced phosphene production was lower and active motor threshold was higher in MWA compare to healthy individuals, suggesting cortical hypoexcitability in migraine (Afra et al., 1998b). One explanation of such controversy is that the cortical response property in migraine is a more complex issue (Coppola et al., 2007), which is exemplified by the lack of habituation in migraine (Afra et al., 2000a; Afra et al., 1998a).

Importantly, our results call attention to investigate patients with and without aura symptoms in separate groups. Only the patients experiencing aura symptoms were the ones who had higher amplitude BOLD fluctuation in our study. This was true for the amplitude of the resting activity and also for the amplitude of the activity of the RSNs.

Several researches investigated the brain resting fMRI activity in migraine with various approaches (Datta et al., 2013; Hadjikhani et al., 2013; Hougaard et al., 2014; Mainero et al., 2011b; Russo et al., 2012; Tedeschi et al., 2015; Tessitore et al., 2015; Tessitore et al., 2013). These approaches are not giving direct information on the cortical hyperexcitability, but a measure of functional interaction. A few studies investigated the amplitude of the resting state BOLD fluctuation in chronic pain conditions (Baliki et al., 2014; Ma et al., 2015) and found higher amplitude of resting activity in chronic back pain, irritable bowel syndrome, knee osteoarthritis and complex regional pain syndrome. Only single study investigated the

amplitude of the low frequency fluctuations in 24 migraineurs, without grouping the patients based on the aura symptoms (Wang et al., 2016).

Recently, the focus of attention has shifted to investigate the activity of resting state fluctuations in various frequency bands (Gao et al., 2015), especially in pain conditions (Kim et al., 2013; Otti et al., 2013). The importance of the various frequencies of BOLD fluctuations is not yet known. It was proposed that functional connectivity of various brain regions are represented in different dominant frequency bands (Salvador et al., 2008). This could be responsible for the alterations found in different frequency bands in the attention network and the cerebellar network. Another option might be that CH and migraine was proposed to be a neurovascular disease, and the altered neurovascular coupling may affect the frequency of the resting BOLD fluctuations (Malinen et al., 2010a; Malinen et al., 2010b) by acting as a filter. Furthermore, the group difference in the RSN activity might well be the result of improved signal to noise ratio by filtering out the low and high frequency artefact. Since most of the slow frequency fluctuation in our analysis with a relatively long TR were shown to be neural origin (Boyacioglu et al., 2013a), this hypothesis seems rather unlikely.

Another important aspect of our result is the spatial distribution of differences. As mentioned we found increased amplitude or resting BOLD fluctuation in the cerebellum, cingulate cortex, parietal lobule and frontal cortex. These results are in agreement with further resting state fMRI studies of CH and migraine (Chou et al., 2017; Rocca et al., 2010). These regions are possibly part of the pain matrix elements (Lee and Tracey, 2013). The anterior cingulate cortex could be a key area of the central sensation of the pain (Davis and Moayedi, 2013; Spisak et al., 2017).

Interestingly, in case of CH our result showed no functional connectivity or amplitude changes in hypothalamus. However, areas we found to have altered connectivity are in structural or functional connection with the hypothalamus. Lemaire's research group found structural white matter connection between the prefrontal cortex and the antero-ventral hypothalamus using diffusion tractography (Lemaire et al., 2011). In the same investigation white matter connections were found between cerebellum and the hypothalamus. Similar hypothalamo-cortical (Risold et al., 1997) and hypothalamo-cerebellar (Dietrichs and Haines, 2002) connections were shown in previous rodent experiments. The structural connection of hypothalamus and frontal cortex strengthened by postoperative investigations of chronic CH

patients. Probabilistic tractography found connection between the effective places of stimulation and the medial lemniscus, frontal cortex, cerebellum and the brainstem trigeminal nuclei (Akram et al., 2017; Owen et al., 2007). DBS stimulation not just influenced the function of the stimulated structures, but also caused structural changes, in effective DBS stimulation hypothalamus showed increased volume (Akram et al., 2017). Other volumetric studies found atrophy in CH in the frontal areas (Absinta et al., 2012; Naegel et al., 2014). They hypothesized, these regions are the part of the pain processing system, and therefore the atrophy is the part of pain related pathomechanism. It is important to note that our findings seem to be in accordance with the volumetric studies; even though our analysis did not reveal hypothalamic activity changes in CH patients. While several studies indicated the important role of the hypothalamus in CH (May et al., 1998, 2000; Morelli et al., 2009; Qiu et al., 2015b; Qiu et al., 2013; Rocca et al., 2010; Sprenger et al., 2004; Yang et al., 2014), it is still debated if it actively contributes to the attacks or the altered hypothalamic activation is secondary to the cortical and subcortical malfunction of the pain matrix.

## Conclusion

Our studies revealed changes in the connectivity of the RSNs in specific frequency bands. The amplitude of fluctuation also showed alterations. The amplitude changes in MWA and in CH also suggest cortical hyperexcitability. Furthermore, the area of alteration localized in the elements of the pain matrix, as indicates differences in the pain processing in both headache disorder. In CH according to our finding, the changes attaching strictly to the headache side. Longitudinal studies are also needed, to reveal the dynamics of the amplitude changes. Even more, correlation between molecular markers could be also impressive, allow us to get depth understanding in the patomechanism of the primary headache disorders.

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