Office use only
Application code: APGE18

IN CONFIDENCE

APPLICATION FOR A PILOT GRANT IN EPILEPSY

Applicants must email one signed copy of the completed form, in Word format, to Caoimhe Bennett (caoimhe@eruk.org.uk). Separate, scanned signature pages in pdf format are acceptable.

Application deadline: Friday 28th September 2018, 16:00

Important notes

- Our pilot grants in epilepsy are up to **£30,000**, over a maximum of **two years**
- Please read the updated '***Information for applicants***' carefully before completing this form. Any application that does not fully comply with the guidance will be rejected
- This is the application form for **pilot grants in epilepsy only**
- Please direct any enquiries to Caoimhe Bennett, Research & Information Manager, Epilepsy Research UK (tel: 020 8747 5024; email: caoimhe@eruk.org.uk)
- Please indicate (by underlining) where you heard about our pilot grants in epilepsy: ERUK website / ERUK Research Register / other (please specify):

PROJECT SUMMARY

Project details

Project title*	Thalamic GABA in childhood and juvenile absence epilepsy
Duration of grant *(in months)**	24
Proposed start date (dd/mm/yyyy) Not before 01/07/19	01/10/2019
Total grant requested*	£ 30,000

Details of principal applicant

Title*	Prof
Surname*	Crunelli
Forename*	Vincenzo
Position*	Professor of Neuroscience

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

Department*	Neuroscience Division - School of Bioscience
Host institution*	Cardiff University
Address	Museum Avenue
City/town*	Cardiff
Postcode	CF10 3AX
Telephone no.	029 2087 4091
Email	crunelli@cardiff.ac.uk

Details of co-applicant 1

Title*	Prof
Surname*	Wise
Forename*	Richard
Position*	Head of MRI
Institution*	CUBRIC (Cardiff University Brain Imaging Centre) Cardiff University
Email	wiserg@cardiff.ac.uk

Details of co-applicant 2

Title*	Dr
Surname*	Hamandi
Forename*	Khalid
Position*	Consultant Neurologist and Honorary Senior Lecturer
Institution*	The Alan Richens Welsh Epilepsy Centre Cardiff and Vale University Health Board
Email	hamandik@cf.ac.uk

Details of co-applicant 3

Title*	Dr
Surname*	Brazzo
Forename*	Daniela
Position*	Clinical Research Fellow and Consultant Child and Adolescent Psychiatrist
Institution*	The Alan Richens Welsh Epilepsy Centre Cardiff and Vale University Health Board
Email	daniela.brazzo@wales.nhs.uk

Details of co-applicant 4

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

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IN CONFIDENCE

Title*	
Surname*	
Forename*	
Position*	
Institution*	
Email	

Please include details of any further co-applicants on an additional sheet.

COLLABORATORS

Please note that if your proposal includes an essential collaboration with a partner that is not a co-applicant, we require a signed letter of commitment to the project from this person.

PROJECT SUMMARIES

Abstract* *(no more than 200 words; in scientific style)*

In different models of absence seizures (ASs) an increased tonic GABA-A receptor-mediated inhibition in thalamic neurons is sufficient for the expression of ASs. In genetic models, this enhanced tonic inhibition results from increased levels of GABA that in turn originate from a selective loss-of-function in GAT-1, one of the GABA transporters. Similar, though indirect, evidence in humans indicates that vigabatrin and tiagabine, two antiepileptic drugs that increase GABA levels, can aggravate ASs and induce them in normal individuals. Moreover, higher levels of GABA were found in the ipsilateral thalamus of a child with atypical monolateral presentation of spike-and-wave discharges, the characteristic EEG signature of ASs.

Our study will use MRI spectroscopy with a 7T scanner to compare GABA levels in thalamus and occipital cortex of Childhood and Juvenile Absence Epilepsy (CAE, JAE) patients with those of age-matched controls. These results will provide pilot data for a larger study aimed at investigating whether abnormal GABA levels in different brain regions of CAE and JAE patients are a consistent phenotype of these epilepsies, have predictive value for the response to various anti-absence medications and for the presence/development of neuropsychiatric or psychological comorbidity seen in these young populations.

Plain English title*

Do children and teenagers with absence seizures have different brain levels of the brain chemical GABA compared to the general population?

Plain English description*

*In no more than **200 words**, please include: (1) why this area of knowledge is worth investigating; (2) what question you're trying to answer; (3) what this research is expected to add to our knowledge of epilepsy; (4) how quickly the results will be applicable to patients: short term (within 12 months), medium term (3-5 years) or long term (10 years or more).*

In contrast to the classical view that decreased inhibition and/or increased excitation underlies epileptic seizures, an elevated concentration of the inhibitory neurotransmitter GABA in the thalamus of different animal models of absence seizures (ASs) is sufficient for the generation of these non-convulsive seizures. Indeed, higher GABA levels were reported in the ipsilateral thalamus of a child with atypical monolateral presentation of spike-and-wave discharges, the characteristic electroencephalographic signature of ASs.

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IN CONFIDENCE

Our study will use MRI spectroscopy with a 7T scanner to compare GABA levels in two brain regions of Childhood and Juvenile Absence Epilepsy (CAE, JAE) patients with those of age-matched controls. These results will provide the necessary preliminary data for a larger study aimed at investigating whether abnormal GABA levels in different brain regions of CAE and JAE patients are a consistent phenotype of these epilepsies, have predictive value for the response to various anti-absence medications and for the presence/development of neuropsychiatric comorbidity. Ultimately, these data will in the medium-term inform the development of novel drugs that selectively target the aberrant mechanisms responsible for increased GABA levels in (sub)populations of CAE/JAE patients and potentially control both ASs and their co-morbidities.

DETAILED DESCRIPTION OF PROJECT

*No more than **750** words (excluding references), please include: (1) a brief background; (2) aims and hypotheses if appropriate; (3) details of the plan and methodology, (4) a timeline and milestones; (5) expected outcomes and relevance to people with epilepsy. **Do not include figures or tables**. **Please use no more than 10 references** and include them in the box headed 'References'.*

If this or a similar proposal has previously been submitted to ERUK and has been rejected NO
…., please ensure you indicate how it has changed since the previous submission.

BACKGROUND

Absence seizures (ASs) are the hall mark of the Idiopathic Generalised Epilepsy sub-syndromes Childhood and Juvenile Absence Epilepsy (CAE, JAE). They are not associated with metabolic/neuropathological deficits [1]. CAE/JAE are genetically determined and may represent complex channelopathies of multi-factorial genetic background, as indicated by genetic abnormalities in various neuronal voltage- and transmitter-gated channels of affected children/teenagers [2].

Although CAE/JAE were in the past considered relatively benign, they have now been shown to be associated with cognitive and neuropsychiatric co-morbidity [3]. Moreover, the failure of monotherapy with gold-standard anti-absence drugs, i.e. valproate and ethosuximide, in 50% of children [4] and the persistence of cognitive impairments even after seizure suppression [3] demand novel therapeutic approaches and a deeper mechanistic understanding of ASs.

In different pharmacological and genetic models of ASs an increased tonic GABA-A receptor-mediated inhibition in thalamic neurons is sufficient for the expression of ASs [5]. In genetic models, this enhanced tonic inhibition results from increased levels of GABA that in turn originate from a selective loss-of-function in GAT-1, one of the GABA transporters [5,6]. Similar, though indirect, evidence in humans indicates that vigabatrin and tiagabine, two antiepileptic drugs that increase GABA levels, can aggravate ASs and induce them in normal individuals [7]. Moreover, higher levels of GABA were found in the ipsilateral thalamus of a child with atypical monolateral presentation of spike-and-wave discharges, the characteristic EEG signature of ASs [8].

AIMS AND HYPOTHESIS

The main hypothesis of our proposed work is that GABA levels in thalamus and occipital cortex (two brain regions that are key for the expression of ASs) of children and teenagers with CAE/JAE are different from those of age-matched normal cohorts. Thus, the main aim of this pilot grant is to establish the optimal recording conditions for MRI spectroscopy in children and adolescents in epilepsy and normal populations and to collect data to establish the variability and differences in GABA levels in these brain regions.

PLAN AND METHODOLOGY

A. Identification of suitable cohort

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

Taking advantage of a currently running Wales-wide audit of CAE and JAE, we will be able to identify suitable individuals for our project. In addition, our local paediatric neurologists generally diagnose 25 new cases of CAE/JAE per year. We have previous successful experience in recruiting similar cohorts [9].

B. MRI scans

The Cardiff University Brain Imaging Centre (CUBRIC) has already implemented a programme of structural brain imaging in children aged 12 and above at 7T demonstrating the feasibility of imaging this age group.
We would collect MRS data at 7T (Siemens Magnetom) to boost our sensitivity to measure GABA concentration in brain tissue. We would use a MEGA semi-LASER acquisition scheme [10] to yield estimates of GABA concentration using 2 voxels (approximately 25x25x25mm), one in the thalamus and one in the occipital cortex. High-resolution structural MRI scans would also be acquired for tissue-type partial volume corrections. Two MRI scanning sessions will be perfomed with an interval of at least a month, with each lasting up to 1 hour.

TIMELINE

A. Recruitment of suitable cohorts will start in October 2019 and most likely end by April 2021.

B. Scanning will start as soon the first few subjects have been enrolled and most likely end by June 2021.

OUTCOMES AND RELEVANCE TO PEOPLE WITH EPILEPSY

There are currently no imaging markers of CAE/JAE, or in fact any of the Idiopathic Generalised Epilepsies at the single subject level, with the diagnoses being based on clinical history and EEG. Similarly, there are no markers that best determine treatment choice, treatment outcome or long term prognosis. Thalamic GABA MRS is an obvious candidate biomarker in CAE/JAE where the technology now exists for these measurements. Furthermore this will have potential across other epilepsies where the thalamus has a role, for example JME and secondary generalised seizures.

References

Please include your references here (no more than 10).

1. Wolf P, Beniczky S. (2014) Understanding ictogenesis in generalized epilepsies. *Expert Rev Neurother*. 14:787-98.
2. Crunelli V, Leresche N (2002) Childhood absence epilepsy: genes, channels, neurons and networks. *Nat Rev Neurosci*. 3:371-82.
3. Loughman A, Bowden SC, D'Souza WJ (2017) A comprehensive assessment of cognitive function in the common genetic generalized epilepsy syndromes. *Eur J Neurol*. 24:453-60.4.
4. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Adamson PC; Childhood Absence Epilepsy Study Team (2013) Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. *Epilepsia* 54:141-55.
5. Cope DW, Di Giovanni G, Fyson SJ, Orbán G, Errington AC, Lorincz ML, Gould TM, Carter DA, Crunelli V (2009) Enhanced tonic GABA-A inhibition in typical absence epilepsy. *Nat Med* 15:1392-98.
6. Pirttimaki T, Parri HR, Crunelli V (2013) Astrocytic GABA transporter GAT-1 dysfunction in experimental absence seizures. *J Physiol*. 591:823-33.
7. Perucca E, Gram L, Avanzini G, Dulac, O (1998) Antiepileptic drugs as a cause of worsening seizures. *Epilepsia* 39:5-17.
8. Leal A, Vieira JP, Lopes R, Lopes da Silva F, Figueiredo D (2016) Dynamics of epileptic

activity in a case of childhood absence epilepsy and correlation with thalamic levels of GABA. *Epil Beh* 5:57-65.

9. Koelewijn L, Hamandi K, Brindley LM, Brookes MJ, Routley BC, Muthukumaraswamy SD, Williams N, Thomas MA, Kirby A, Te Water Naudé J, Gibbon F, Singh KD (2015) Resting-state oscillatory dynamics in sensorimotor cortex in benign epilepsy with centro-temporal spikes and typical brain development. *Hum Brain Mapp*. 36:3935-49.
10. Andreychenko A, Boer VO, Arteaga de Castro CS, Luijten PR, Klomp DWJ (2012) Efficient spectral editing at 7 T: GABA detection with MEGA-sLASER. *Magn Reson Med*. 68:1018-1025.

Did you consult a qualified statistician when preparing this application? If so, please briefly outline their involvement and contribution (no more than 100 words):

A qualified statistician is not required for this pilot grant. We will use descriptive and inferential statistics for comparison between groups, that is well within the expertise of the applicant team.

What makes this a pilot grant rather a project grant (no more than 50 words)?

Except for a case report [8], no study has investigated GABA levels in CAE/JAE, and none with a 7T scanner. This study will assess i) acceptability-tolerability of scans to optimise future acquisitions ii) range of GABA levels in patients and normal subjects, iii) differences between normal and epileptic populations and iv) the stability of measurements across repeat scans.

RISKS AND CONTINGENCIES

Please outline (1) the possible risks posed by your methodology and (2) any contingency plans that you have (or will have) in place (no more than 200 words):

1) Recruitment – we will engage widely with a network of paediatric epileptologists who already work closely together in a current audit of CAE and JAE in Wales. We think the risk of failure to recruit 10 children with CAE in the timeframe of the award is very low, and we are adequately resourced to deliver this number. Our contingency plan will be to include and disseminate widely at the start of the award.
2) 7T MRI – scanning children is more challenging than adults because of the need for the participants to keep their heads very still during data acquisition. CUBRIC has already performed structural MRI scanning at 7T in children demonstrating feasibility. This project will yield information about the quality and repeatability of MRS data from children's brains. To reduce the chances of data corruption through head-motion, we would split the voxel acquisitions and carefully exclude repetitions, within session, of poor quality, a process for cleaning MRS data.

PUBLIC AND PATIENT INVOLVEMENT (PPI)

Have you considered the principles of PPI in the design of your project?	Yes	X	No	

If yes, please provide more details (no more than 50 words):

We have worked closely with Epilepsy Action Cymru and Epilepsy Wales over many years, and more recently with the Health and Care Research Wales-funded BRAIN Units, BRAIN Involve (http://brain.wales/get-involved/brain-involve/) and Involving people (invo.org.uk) groups.

DISSEMINATION OF FINDINGS

Please outline how you plan to disseminate your findings to Epilepsy Research UK stakeholders and other non-scientific audiences (no more than 75 words):
All applicants are regularly involved in delivering lectures to non-scientific audiences both in the UK and abroad. In particular, K. Hamandi gives regular talks to meetings organised by Epilepsy Action Cymru and Epilepsy Wales, and recent ER-UK information days. CUBRIC has an active public engagement programme including Brain Games and primary school assemblies. V. Crunelli provides yearly lectures to epilepsy patients, patient-support groups and the general public in the UK, Malta and Italy. D. Brazzo gives public engagement talks in CUBRIC.

RESEARCH PROGRESSION

Please outline what the next step after this pilot project would be (in terms of research progression) (no more than 100 words):
Application for a full project grant either to ERUK or MRC.

INDEPENDENT REFEREES

Please suggest up to two independent referees who would be suitable to review your application *(please supply name, institution and email address)*:

Reviewer 1	Prof. Hal Blumenfeld Director Yale Clinical Neuroscience Imaging Center Yale University Medical School New Haven USA hal.blumenfeld@yale.edu Prof. Blumenfeld is a consultant neurologist and world-leader in clinical and experimental research on absence seizures.
Reviewer 2	Prof Richard A Edden FM Kirby Center for Functional Brain Imaging Department of Radiology & Radiological Science Johns Hopkins University School of Medicine Baltimore USA raee2@jhu.edu Prof Edden is a world-leading expert in human GABA spectroscopy

Epilepsy Research UK may contact both, one or neither of these nominees

If there is anyone you would rather we didn't invite to review your application, please give their details here *(no more than two; please supply name and institution)*:

Nominee 1	

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

IN CONFIDENCE

Nominee 2	

Epilepsy Research UK will undertake not to contact these nominees

APPLICANT DETAILS – PRINCIPAL APPLICANT

*Please nominate **one** principal applicant only. This person should be a representative of the host institution where the majority of the research will be performed. Correspondence concerning the grant will be sent to this individual.*

Title*	Prof		
Surname*	Crunelli		
Forename*	Vincenzo		
Department*	Neuroscience Division – School of Bioscience		
Institution*	Cardiff University		
Address 3	Museum Avenue		
Address 4			
City/town*	Cardiff	Postcode	CF10 3AX
Telephone no.	029 2087 4091	Fax	N/A
Email	crunelli@cardiff.ac.uk		
Current post (job title)*	Professor of Neuroscience		
Date of appointment	1 Nov 1991		

Qualifications *(please list most recent first and add lines as necessary)*

Date of qualification	Type of qualification	Awarding body
July 1974	Laurea (110/110 cum laude)	University of Catania, Catania, Italy

Last three posts held *(please list most recent first)*

Job title	Institution	Date of appointment
Head, Neuroscience Division	Cardiff University	2002-2016
Head, Physiology Department	Cardiff University	1993-1998
Senior Lecturer	University of London	1989-1991

Five most relevant and/or significant peer-reviewed publications *(most recent first; please supply full citation).* ***These must be published or accepted*.**

1	McCafferty C, David F, Venzi M, Orban G, Lőrincz ML, Atherton Z, Recchia G, Lambert RC, Leresche N, Di Giovanni G, Delicata F and Crunelli V. Cortical drive and thalamic feed-forward inhibition control thalamic output synchrony during absence seizures. **Nature Neuroscience**, 21 (2018) 744-756.
2	David F, Çarçak N, Furdan S, Onat F, Gould T, Mészáros Á, Di Giovanni G, Hernández VM, Chan CS, Lőrincz ML, Crunelli V. Suppression of hyperpolarization-activated cyclic nucleotide-gated channel function in thalamocortical neurons prevents genetically determined and pharmacologically induced absence seizures. **Journal of Neuroscience**, 38 (2018) 6615-6627.

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

3	McCafferty C, Connelly WM, Celli R, Ngomba RT, Nicoletti F, Crunelli V. Genetic rescue of absence seizures. **CNS Neuroscience & Therapeutics**, 24 (2018) 745-758.
4	Pirttimaki T, Parri HR, Crunelli V. (2013). Astrocytic GABA transporter GAT-1 dysfunction in experimental absence seizures. **Journal of Physiology**, 591 (2013) 823-833.
5	Cope DW, Di Giovanni G, Fyson SJ, Orban G, Errimgton AC, Lorincz ML, Gould TM, Carter DA, Crunelli V. Enhanced tonic $GABA_A$ inhibition in typical absence seizures. **Nature Medicine**, 15 (2009) 1392-1398.

Time contribution to project per week *(hrs)*	2
Source of current salary support	HEFCW
Are you applying for your own salary support?	No

APPLICANT DETAILS – CO-APPLICANT 1

Title*	Prof		
Surname*	Wise		
Forename*	Richard		
Department*	CUBRIC		
Institution*	Cardiff University		
Address 3	Maindy Road		
Address 4			
City/town*	Cardiff	Postcode	CF24 4HQ
Telephone no.		Fax	
Email	wiserg@cardiff.ac.uk		
Current post (job title)*	Head of MRI (CUBRIC)		
Date of appointment	1 October 2006		

Role in project, including time contribution (hrs) per week (no more than 50 words):

Implementation and management of MR data acquisition and analysis, working with CUBRIC MRS post-docs. (2 hours/week)

Qualifications *(please list most recent first and add lines as necessary)*

Date of qualification	Type of qualification	Awarding body
1998	PhD	University of Cambridge
1994	BA Hons (Natural Sciences: Physics and Theoretical Physics)	University of Cambridge

Last three posts held *(please list most recent first)*

Job title	Institution	Date of appointment
CUBRIC, Director of MRI (Reader 2006-2009 Prof 2009-present)	CUBRIC (Cardiff University Brain Imaging Centre	2006-2016

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MRC Career Development Fellow	FMRIB, Oxford University	2005 - 2006
Wellcome Trust Advanced Training Fellow	FMRIB, Oxford University	2002 - 2005

Five most relevant and/or significant peer-reviewed publications *(most recent first; please supply full citation).* ***These must be published or accepted*****.**	
1	Merola A, Germuska MA, Warnert EA, Richmond L, Helme D, Khot S, Murphy K, Rogers PJ, Hall JE, Wise RG. (2017) Mapping the pharmacological modulation of brain oxygen metabolism: the effects of caffeine on absolute CMRO(2) measured using dual calibrated fMRI. **Neuroimage** 155:331-343.
2	Warnert EA, Rodrigues JC, Burchell AE, Neumann S, Ratcliffe LE, Manghat NE, Harris AD, Adams Z, Nightingale AK, Wise RG, Paton JF, Hart EC. (2016) Is High Blood Pressure Self-Protection for the Brain? **Circ Res** 119:e140-e151.
3	Germuska M, Merola A, Murphy K, Babic A, Richmond L, Khot S, Hall JE, Wise RG. (2016) A forward modelling approach for the estimation of oxygen extraction fraction by calibrated fMRI. **Neuroimage**. 139:313-323.
4	Gili T, Saxena N, Diukova A, Murphy K, Hall JE, Wise RG. (2013) The thalamus and brainstem act as key hubs in alterations of human brain network connectivity induced by mild propofol sedation. **Journal of Neuroscience**. 33:4024-4031.
5	Harris AD, Roberton VH, Huckle DL, Saxena N, Evans CJ, Murphy K, Hall JE, Bailey DM, Mitsis G, Edden RA, Wise RG. (2013) Temporal dynamics of lactate concentration in the human brain during acute inspiratory hypoxia. **J Magn Reson Imaging**. 37:739-745.

Source of current salary support	HEFCW
Are you applying for your own salary support?	No

APPLICANT DETAILS – CO-APPLICANT 2

Title*	Dr		
Surname*	Hamandi		
Forename*	Khalid		
Department*	The Alan Richens Welsh Epilepsy Centre		
Institution*	Cardiff and Vale University Health Trust		
Address 3	Heath Park		
Address 4			
City/town*	Cardiff	Postcode	CF14 4XW
Telephone no.		Fax	
Email	hamandi@cardiff.ac.uk		
Current post (job title)*	Consultant Neurologist and Honorary Senior Lecturer		
Date of appointment	11 September 2006		

Role in project, including time contribution (hrs) per week (no more than 50 words):

I am the senior clinician and epileptologist on the team. I will provide advice and support on protocol development, recruitment and NHS ethics and R&D approvals; and interpretation, dissemination of findings and development of future applications. (0.5 hours per week.)

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Qualifications *(please list most recent first and add lines as necessary)*		
Date of qualification	Type of qualification	Awarding body
2008	PhD	London University
1997	MRCP	Royal College of Physicians
1994	MB BS	London University
1991	BSc	London University
Last three posts held *(please list most recent first)*		
Job title	Institution	Date of appointment
Neurology Specialist Registrar	Royal United Hospital Trust, Bath	January 2006 - Aug 2006
Clinical Research Fellow	University College London, Institute of Neurology	January 2003 - December 2005
Neurology Specialist Registrar	North Bristol NHS Trust	March 2000 - December 2002

Five most relevant and/or significant peer-reviewed publications *(most recent first; please supply full citation).* ***These must be published or accepted*****.**	
1	Powell R, Elwes R, Hamandi K, Mullatti N. (2018) Cingulate gyrus epilepsy. **Pract Neurol**. [Epub ahead of print] PMID:30100562.
2	Kopczynska M, Zelek WM, Vespa S, Touchard S, Wardle M, Loveless S, Thomas RH, Hamandi K, Morgan BP (2018). Complement system biomarkers in epilepsy. **Seizure** 60:1-7.
3	Routley B, Hamandi K, Singh KD, Muthukumaraswamy SD (2017). The effects of AMPA receptor blockade on resting MEG recordings. **Journal of Psychopharmacology**. 31:1527-1536.
4	Kirby A, Williams N, Koelewijn L, Brindley LM, Muthukumaraswamy SD, Te Water Naudé J, Thomas M, Gibbon F, Singh KD, Hamandi K. (2017) Benign childhood epilepsy with centrotemporal spikes (BECTS) and developmental co-ordination disorder. **Epilepsy Behaviour**. 72:122-126.
5	Hamandi K, Routley BC, Koelewijn L, Singh KD. (2015) Non-invasive brain mapping in epilepsy: Applications from magnetoencephalography. **J Neurosci Methods**. 260:283-291.

Source of current salary support	NHS
Are you applying for your own salary support?	No

APPLICANT DETAILS – CO-APPLICANT 3

Title*	Dr
Surname*	Brazzo
Forename*	Daniela
Department*	The Alan Richens Welsh Epilepsy Centre
Institution*	Cardiff and Vale University Health Board
Address 3	Heath Park

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

Address 4			
City/town*	Cardiff	Postcode	CF14 4XW
Telephone no.		Fax	
Email	daniela.brazzo@wales.nhs.uk		
Current post (job title)*	Clinical Research Fellow and Consultant Child and Adolescent Psychiatrist		
Date of appointment	April 2018		

Role in project, including time contribution (hrs) per week (no more than 50 words):

As a consultant child psychiatrist with expertise in epilepsy and a clinical research fellow in epilepsy, I will provide advice and support on protocol development, recruitment, NHS ethics and R&D approvals. I will also provide support in the interpretation, dissemination of findings and development of future applications. (1 hour per week.)

Qualifications *(please list most recent first and add lines as necessary)*

Date of qualification	Type of qualification	Awarding body
2011	PhD	Aston University
2007	Specialist Training in Child and Adolescent Neuropsychiatry	Pavia University, Italy
2002	MD	Pavia University, Italy

Last three posts held *(please list most recent first)*

Job title	Institution	Date of appointment
Clinical Research Fellow in Epilepsy	Cardiff University	April 2108 - to date
Consultant Child and Adolescent Psychiatrist	St David's Hospital, Cardiff, Cwm Taf Health Board	September 2016 - to date
Consultant Child and Adolescent Psychiatrist	Princess of Wales Hospital, Bridgend, Cwm Taf Health Board	April 2013- August 2016

Five most relevant and/or significant peer-reviewed publications *(most recent first; please supply full citation).* ***These must be published or accepted*.**

1	MC Pera, D Brazzo, N Altieri,U Balottin,P Veggiotti (2013) Long-term evolution of neuropsychological competences in encephalopathy with status epilepticus during sleep: a variable prognosis. **Epilepsia**. 54 Suppl 7:77-85.
2	P. Veggiotti, MC. Pera, F. Teutonico, D Brazzo, U. Balottin, CA. Tassinari (2012) Therapy of Encephalopathy with Status Epilepticus during Sleep (ESES-CSWS syndrome): an update. **Epileptic disorders**. 14:1-11.
3	D. Brazzo, G. Di Lorenzo, P. Bill, M. Fasce, G. Papalia, P. Veggiotti, S. Seri (2011). Abnormalities of visual sensory gating in pediatric photosensitive epilepsy. **Clin Neurophysiol**. 122:16-20.
4	F. Ragona, D. Brazzo, I. De Giorgi, M. Morbi, E. Freri, F. Teutonico, E. Gennaro, F. Zara, S. Binelli, P. Veggiotti, T. Granata (2010). Dravet syndrome: early manifestations and cognitive outcome in 37 Italian patients. **Brain and Dev.** 32:71-7.
5	S. Seri, NJ Thai, D. Brazzo, F. Pisani, A. Cerquiglini (2009). Neurophysiology of CSWS-

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

	associated cognitive dysfunction. **Epilepsia**. 50:33-36.
Source of current salary support	Cardiff University - NHS
Are you applying for your own salary support?	No

LICENSING DETAILS

Experiments on animals

Does your proposed project involve the use of animals?	Yes		No	X
If yes, does your project include procedures to be carried out in the UK which require a Home Office licence?	Yes		No	
If yes, has the Home Secretary granted a Project licence, under the terms of the Animals (Scientific Procedures) Act 1986, authorising the experiments?	Yes		No	

If yes, please state:	
Name of licensee	
Address of licensee	
Project Licence reference no	
Date of issue	
End date	
I, the licence holder, agree that the work outlined in this proposal can be completed under this licence (please sign)	Signature Printed name, including title
If the proposal includes procedures that require a Home Office licence but one has not been granted, it must be applied for and granted (and proof provided to Epilepsy Research UK) before any funds can be released.	

Research on human participants or human tissue

Does your research involve the use of human participants or human tissue?	Yes	X	No	

If yes, please list all of the regulatory/ethical approvals that you require to conduct this research. For each, please indicate the issuing body and the current status of the approval (already in place/application submitted/yet to apply). For approvals that are already in place, please provide details (including a reference number if available and expiry date).

Please note: clinical research projects utilising NHS premises, staff or patients require a signature from or on behalf of the Head of R&D at the lead NHS site prior to submission of the application (see *'Declarations'* below):

This proposal will require NHS Ethics and R&D approval.

This will be along similar lines to an existing ethics approval for brain imaging in patients with epilepsy in CUBRIC – reference 08/H0102/12.

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

IN CONFIDENCE

All approvals must be in place (and proof provided to Epilepsy Research UK) before any funds can be released.

Intellectual property

Does your project have potential or actual commercial applications?	Yes		No	X
If yes, please describe what these are/may be *(no more than 100 words)*:				

Possible time scale of commercial exploitation *(please tick box)*					
Already exploited		Within 12 months		1-3 years	
3-5 years		5-10 years	X	More than 10 years	

RELEVANT EXPERIENCE

Please list the five <u>most relevant</u> grants held, or previously held, by you and your co-applicants:

Period	Project title	Sum	Applicant	Awarded by
2015 - 2020	The Wales Brain Repair and Intracranial Neurotherapeutics (BRAIN) Unit	£1.2M	Hamandi (Co-applicant with 18 colleagues)	Health Care Research Wales. Wales Government
2013 - 2018	Building multi-site clinical research capacity in Magnetoencephalography (MEG)	£1.3M	Hamandi (Co-applicant with 11 colleagues)	MRC/EPSRC
2009-2011	Spatio-temporal firing dynamics of cortical and thalamic neurons during typical absence seizures	£ 336,054	Crunelli	MRC
2012-2014	Serotoninergic modulation of absence seizures: focus on tonic GABA-A inhibition in the thalamus	£149,827	Crunelli (Principal Applicant, with 1 colleague)	ERUK
2016-2018	Closed-loop serotonin optogenetic stimulation to suppress epileptic seizures: a therapeutic device	Euro 148,645	Crunelli (Co-applicant with 1 colleague)	Malta Research & Innovation Programme

If you are applying for a clinical research project, please list the clinical studies that you have been involved in in the last five years. For each, please indicate the number of subjects you recruited and whether you reached your recruitment target.

The applicants have been involved in the following clinical studies:

2018 - GWEP1521. A Randomized Controlled Trial of Cannabidiol (GWP42003-P, CBD) for Seizures in Tuberous Sclerosis Complex. GW Pharma. Target 5, recruited 4 to date.

2017 - Biology of Juvenile Myoclonic Epilepsy (BIOJUME). Target 30, recruited 30 to date.

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2017 - BASE: Brivaracetam And Seizure reduction in Epilepsy. Phase 4. UCB Pharma. Target 10, recruited 27 to date.

2015 - 2017. A Global, Postmarketing Observational Safety Study to Evaluate the Safety and Tolerability of Fycompa® (Perampanel) as Add-on Therapy in Epilepsy Patients Aged ≥ 12 Years. Eisai Ltd. Target 10, recruited 33.

2015 - 2017 SANADII. Target 150, recruited 157.

2013 - 2017. MS Society UK: MRI predictors of rehabilitation. Recruited 145 MS patients (target met).

2013 - 2017. EPSRC: Development of methods to map brain oxygen consumption. Recruited 20 MS patients (target met).

FUNDING SOURCE DETAILS

Other grants concurrently held by applicants

Awarding body	Project title	Grant sum	Dates of support	Held by
Medical Research Council	Building multi-site clinical research capacity in Magnetoencephalography (MEG).	£1,500,000	2013 - 2018	Hamandi (co-applicant with 5 colleagues)
Pfizer, ASPIRE	Effect of Tofacitinib on Pain Processing in Rheumatoid Arthritis (ToPPRA)	£331,000	2019-2012	Wise (co-applicant with 2 colleagues)
MRC Confidence in Concept (Cardiff University)	Demonstrating clinical utility of a non-invasive MRI tool to map altered brain oxygen metabolism: proof of concept in epilepsy	£49,884	2017-2018	Wise (co-applicant with 2 colleagues)
MRC	A stem cell model to study human cortical interneuron function	£ 556,602	2014 – 2018	Crunelli (co-applicant with 2 colleagues)
Welcome Trust	Defining endophenotypes from integrated neuroscience	£ 5,340,758	2015 – 2019	Crunelli (co-applicant with 6 colleagues)
European Union	Training, research and raising public awareness in cell biology and pathology of neuroglia	Euro 2,198,920	2017 – 2020	Crunelli (co-applicant with 8 colleagues
Moondance Charitable Fund (Velindre NHS Trust)	An observational study of neurocognitive function in patients undergoing Stereotactic Radiosurgery at Velindre Cancer Centre	£124,362	2016-2018	Wise (co-applicant with 9 colleagues)
Arthritis Research UK	Biomechanics and Bioengineering Centre (Centre renewal grant)	£2,000,000	2016-2021	Wise (co-applicant with 16 colleagues)

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Medical Research Council UK	Characterising brain network differences during scene perception and memory in young adult APOE-e4 carriers: multi-modal imaging in ALSPAC	£1,865,362	2016-2020	Wise (co-applicant with 8 colleagues)
Medical Research Council UK	Partnership Grant, "The UK7T Network: developing the ultra-high field MRI platform for biomedical research"	£1,302,903	2016-2019	Wise (co-applicant with 18 colleagues)
EPSRC	Strategic Equipment Fund. "National Facility for In Vivo MR Imaging of Human Tissue Microstructure"	£2,944,960	2014-2019	Wise (co-applicant with 9 colleagues)
Wellcome Trust	Strategic Award "Multi-Scale and Multi-Modal Assessment of Coupling in the Healthy and Diseased Brain"	£4,900,000	2016-2021	Wise (co-applicant with 10 colleagues)

Funding applications for this project

If this or any related grant is currently being put forward for funding by any other body, please give details: **NO**			
Awarding body	Project title	Grant sum	Date you will be notified of outcome
		£	
		£	
		£	

Please add additional lines as necessary.

ERUK FUNDING HISTORY

Previous or current support from Epilepsy Research UK

Please give details of all Epilepsy Research UK grants that you are/have previously been named on (add lines as necessary):

Principal Investigator	Dates of support	Project title	Grant sum
V. Crunelli	2012-2014	Serotoninergic modulation of absence seizures: focus on tonic GABA-A inhibition in the thalamus	£149,827
Khalid Hamandi	2009-2011	Magnetoencephalographic measures of abnormal sensory oscillations: A new window on photosensitive epilepsy.	£99,980

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

Please add additional lines as necessary.

CONTACT DETAILS OF FINANCE DEPARTMENT

Please give the contact details of the person in your institution's finance department, whom we should notify if your proposal is successful

Title*	Ms		
Surname*	Morris		
Forename*	Elid		
Department*	Research – Grant Division		
Institution*	Cardiff University		
Address 3	Newport Road		
Address 4			
City/Town*	Cardiff	Postcode	CF24 0DE
Tel		Fax	
E-mail	morrise12@cardiff.ac.uk		

Clinical studies must be costed using the AcoRD framework (https://www.amrc.org.uk/costing-clinical-research-acord). Applicants using AcoRD are advised to speak with the designated AcoRD specialist at the Study Support Service of their local Clinical Research Network (https://www.nihr.ac.uk/funding-and-support/study-support-service/). Contact caoimhe@eruk.org.uk for more information.

FINANCIAL DETAILS OF SUPPORT REQUESTED: PROJECT COSTS

	Year 1	Year 2	**Project total**
MRI scans (40 scans, 20 subjects) at £550.00/scan	£ 8,800	£ 13,200	£ 22,000
Travel	£ 600	£ 915	£ 1,515
	£	£	£
	£	£	£
	£	£	£
	£	£	£
	£	£	£
	£	£	£

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

Yearly total	£ 9,400	£ 14,115	**£ 23,515**
	Year 1	Year 2	**Project total**
Species 1: no. required			
Cost	£	£	£
Species 2: no. required			
Cost	£	£	£
Yearly total	£	£	**£**
	Year 1	Year 2	**Project total**
	£	£	£
	£	£	£
	£	£	£
	£	£	£
	£	£	£
	£	£	£
	£	£	£
	£	£	£
Yearly total	£	£	**£**
£			

FINANCIAL DETAILS OF SUPPORT REQUESTED: SALARY COSTS

Full time equivalent (FTE) (%)		
	Year 1	Year 2
Basic salary (at 100% FTE)	£ 43,681	£ 43,972
Location allowance†	£	£
Any other allowance/award/ supplement‡	£	£
NI§ + Superannuation	£ 15,815	£ 15,921
Yearly total (at 100% FTE)	£ 59,496	£ 59,893
Yearly cost *(calculate at 10% x FTE)*	£ 496	£ 5,989
Full time equivalent (FTE) (10%)		
	Year 1	Year 2
Basic salary (at 100% FTE)	£	£
Location allowance†	£	£
Any other allowance/award/ supplement‡	£	£

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NI§ + Superannuation	£	£
Yearly total (at 100% FTE)	£	£
Yearly cost *(calculate at x FTE)*	£	£
Full time equivalent (FTE) (%)		
	Year 1	Year 2
Basic salary (at 100% FTE)	£	£
Location allowance†	£	£
Any other allowance/award/ supplement‡	£	£
NI§ + Superannuation	£	£
Yearly total (at 100% FTE)	£	£
Yearly cost *(calculate at x FTE)*	£	£
Full time equivalent (FTE) (%)		
	Year 1	Year 2
Basic salary (at 100% FTE)	£	£
Location allowance†	£	£
Any other allowance/award/ supplement‡	£	£
NI§ + Superannuation	£	£
Yearly total (at 100% FTE)	£	£
Yearly cost *(calculate at x FTE)*	£	£
Full time equivalent (FTE) (%)		
	Year 1	Year 2
Basic salary (at 100% FTE)	£	£
Location allowance†	£	£
Any other allowance/award/ supplement‡	£	£
NI§ + Superannuation	£	£
Yearly total (at 100% FTE)	£	£
Yearly cost *(calculate at x FTE)*	£	£
		Total project salary costs

† If applicable. ‡ If applicable. Please specify:

§ National Insurance contributions

Total costs year 1	Total costs year 2	**Overall project total**
£ 9,896	£ 20104	£ 30,000

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.

Office use only
Application code: APGE18

IN CONFIDENCE

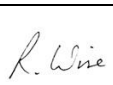
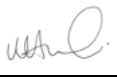
JUSTIFICATION OF SUPPORT REQUESTED

Please describe the need for all materials, consumables, equipment, animals and other items and the role of any member of staff employed on this project (no more than 300 words):
7T MRI scans are costed at £550 per hour. CUBRIC is one of only five 7T MRI systems in the UK. The cost includes maintenance, technical support, radiographer and access to IT facilities for data analysis (CUBRIC computing cluster). Support is requested for a part-time (10% FTE) grade 6 postdoc to analyse the scans and produce results (1 month in year 1 and 12 months in Year 2). Travel (to and from home) for scanned patients and a parent/guardian is also requested.

DECLARATIONS

Principal applicant and co-applicants

I declare that the information in this application is correct to the best of my knowledge and that no relevant information has been withheld. I confirm that I have read Epilepsy Research UK's Terms and Conditions, and the general requirements of grant holders, and undertake to comply with them should this application be successful. I also agree to advise Epilepsy Research UK of any change to my status within the host institution, or any scientific, managerial or administrative issue that might affect the direction of the research. I understand that the Terms and Conditions may change during the tenure of an award and I would then be required to sign my agreement to the new Terms and Conditions or possibly forfeit the grant if I cannot comply.

Signature			
Name	V. Crunelli	Date	18 Sept 2018
Signature			
Name	R. Wise	Date	18 Sept 2018
Signature			
Name	K. Hamandi	Date	18 Sept 2018
Signature			
Name	D. Brazzo	Date	18 Sept 2018

Administrative authority of host institution

On behalf of the host institution, I confirm that the application has been submitted with the agreement of the host institution that will administer the grant, if awarded, and that the grant will be used only to support the work for which it was intended. The host institution is not aware of any relevant information that has been withheld or of any information given in the application that is misleading. On behalf of the host institution, I confirm that I have read and the institution accepts Epilepsy Research UK's Terms and Conditions and that it is the intention of the host institution to maintain support for this department during the period of the grant. The institution understands that the

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IN CONFIDENCE

Terms and Conditions may change during the tenure of an award and the institution would then be required to sign its agreement to the new Terms and Conditions or possibly forfeit the grant if the institution cannot comply.	
Signature	
Name	Elid Morris
Position	Head of Research Grants
Date	18/09/2018

Head of department at host institution

I confirm that I have read and support this application, and that I am not aware of any relevant information that has been withheld or any information given in the application that is misleading. I agree to the research being carried out in my department, and will provide the necessary accommodation and facilities. I confirm all necessary licences and approvals have been obtained or are being sought.	
Signature	
Name	PP. Prof Eshwar Mahenthiralingam
Position	Director of Research on behalf of Head of School
Date	18.9.18

R&D approval at the lead NHS site (clinical research projects only)

I confirm that this study does (tick 'yes')/doesn't (tick 'no') require MHRA approval	Yes	√	No	
I confirm that I have reviewed this proposal.				
Signature				
Name	Christopher Fegan			
Position	R and D Director			
Date	27/9/18			

* If your application is successful, the contents of the marked fields may be published on Epilepsy Research UK's website, and in the charity's annual reports and regular newsletters.