METABOLIGHT

Updates from UCL's ground-breaking project using light to monitor brain activity

03: The hospital issue

Welcome to our third edition of *MetaboLight*. Following the Science and Engineering editions, this is the Hospital edition.

In this publication the MetaboLight team presents the developmental journey of a newborn brain, the common brain issues encountered in this period and how our research is helping to improve the understanding of brain injury in these critically ill babies.

This edition of *MetaboLight* has been published to coincide with our interactive installation being displayed at the Royal Society Summer Science Exhibition, 1–7 July 2019.

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Produced by the MetaboLight team from the UCL Department of Medical Physics and Biomedical Engineering; and funded by the Wellcome Trust

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UCL · wellcome · METABO LIGHT · Design Science · THE ROYAL SOCIETY SUMMER SCIENCE EXHIBITION 1 – 7 JULY 2019

The developing brain

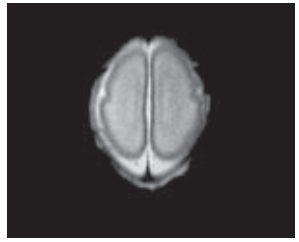
by Joshua Russell-Buckland, PhD student in Mathematical Modelling

Babies' brains differ from adults' in more than just their size. Babies' brains are smoother because the folds develop over time. Within 90 days of birth the brain roughly doubles in volume.

Until the age of three, a baby will form neurons faster than at any other time in its life; they have twice as many neurons at three as they do as an adult. MRI scans of premature babies (pictured) help us understand the development of babies' brains.

3 months

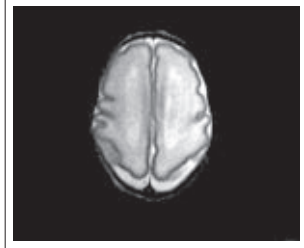
BODY FULLY FORMED



The arms, hands, fingers, feet and toes are fully formed. The baby can open and close its fists and mouth. Organs and extremities are present and will mature to become functional.

6 months

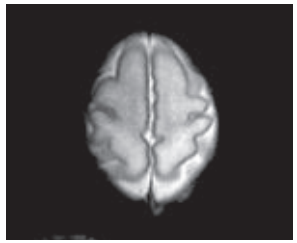
RESPONDS TO SOUNDS



The brain is developing rapidly. Fatty sheaths which transmit electrical impulses along nerves are forming. The baby now responds to sounds.

7 months

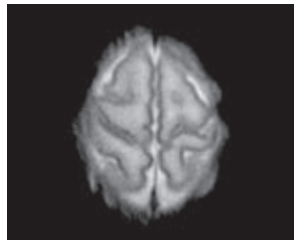
HEARING FULLY DEVELOPED



The baby's hearing is fully developed. The baby now responds to stimuli including sound, pain and light. It can also make grasping motions and starts to suck its thumb.

8 months

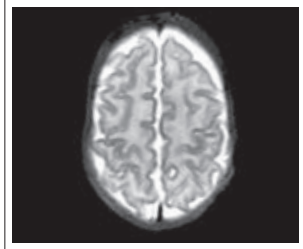
SIGHT FUNCTIONING



The brain continues to develop rapidly and the baby can now see and hear. Most internal systems are well developed but the lungs may still be immature.

9 months

REFLEXES COORDINATED

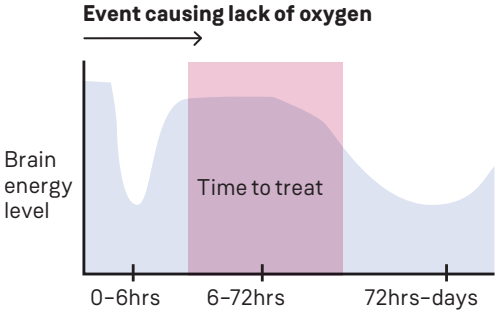


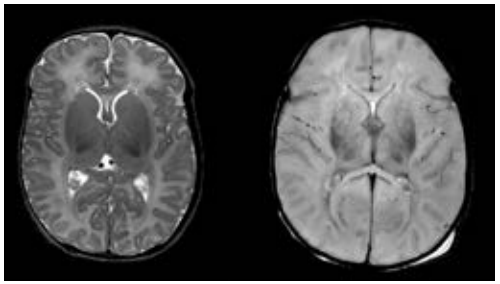
The baby's reflexes are coordinated. It can blink, close its eyes, turn its head, grasp firmly and respond to sounds, light and touch.

Brain injury

by Dr Subhrabrata Mitra, Consultant Neonatologist
and Zuzana Kovacsova, PhD Student in Medical Physics

The newborn brain is a complex, fast developing and therefore fragile environment. Any injury to the brain during this stage can have severe repercussions.
It is crucial to monitor the newborn brain to understand why and how brain injuries happen.





Left: Brain MRI scan from a good outcome baby after moderate damage.
Right: MRI brain scan from a poor outcome baby after severe damage

WHAT IS HIE?

The most common form of brain injury in term infants is hypoxic ischemic encephalopathy (HIE), caused by a lack of blood and oxygen supply to the brain around the time of birth. There are lots of different possible causes of HIE that can happen during birth. It is a life-threatening condition that requires emergency attention.

Following brain injury after HIE, it goes through stages of energy failure leading to the damaged brain cells. The speed of intervention is crucial as there is only a small window to treat HIE (image left).

WHAT ARE THE SYMPTOMS?

The symptoms of HIE depend on the severity of the injury – it can be mild, moderate or severe. Mild symptoms might include behavioural issues, such as hyper alertness or being irritable. In mores severe cases babies will need resuscitation at birth as well as neonatal intensive care support, and they will develop seizures. The symptoms depend on factors such as the severity of the birth, the baby's age and how HIE is managed after birth.

Hypoxic-ischemic encephalopathy (HIE): key facts

1st
Most common form of brain injury in term infants

10%
At least one in ten infants die early in life

50%
Half of the babies will develop serious disabilities by 2 years of age

25%
Responsible for more than a quarter of childhood deaths globally

5th
Fifth leading cause of death worldwide in children under 5 years of age

72h
Only available treatment is to cool baby for 72 hours as soon as possible after birth

Monitoring brain injury

by Paola Pinti, Biomedical Engineer

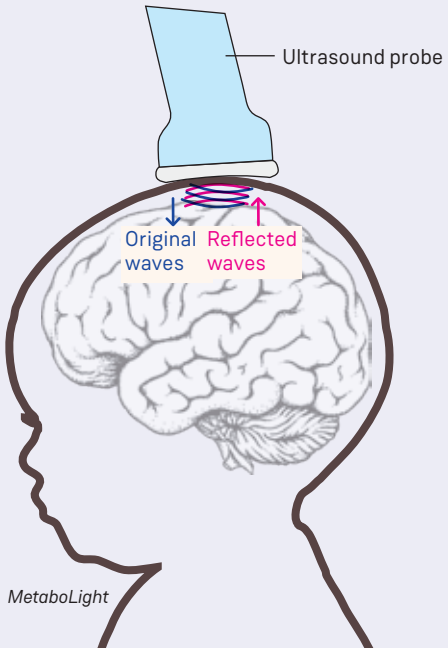
At the neonatal intensive care unit, babies' brains are closely monitored using a range of technologies to identify issues that could affect their development.

1

BRAIN ULTRASOUND

Ultrasound probes transmit and receive high frequency sound waves to create images of organs. The sound wave transmitted by the probe is reflected off the organ. The reflection (or 'echo') is detected by the probe and converted into images by a computer. Babies have a unique advantage as they have a soft spot on their head where the ultrasound probe can be placed to image the brain.

The ultrasound image can identify brain structures. This can be repeated easily and is very helpful to identify brain injuries early on in sick babies, and to monitor progress over time.



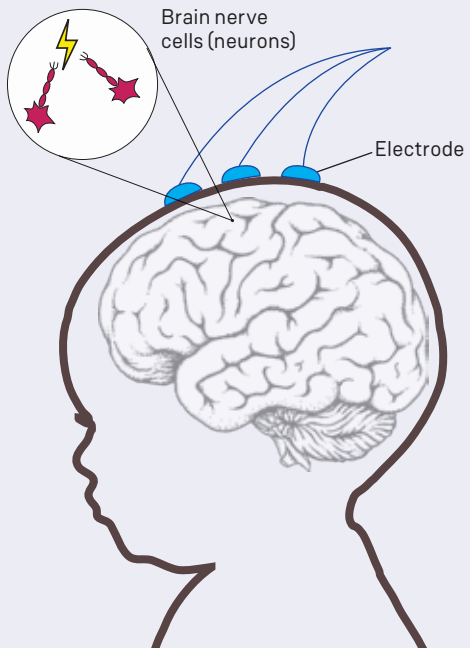
2

ELECTROENCEPHALOGRAM (EEG)

EEGs identify changes in brain function by measuring electrical activity. Billions of nerve cells in your brain produce tiny amounts of electrical activity. EEGs amplify and record the electrical activity on paper.

EEGs help us diagnose conditions and measure symptoms, such as seizures (fits). They can monitor a baby's progress after the brain has been deprived of oxygen and blood.

Amplitude integrated EEG is a compressed version of EEG that is easy to apply and does not need the specialists but lacks in information that EEG can provide.

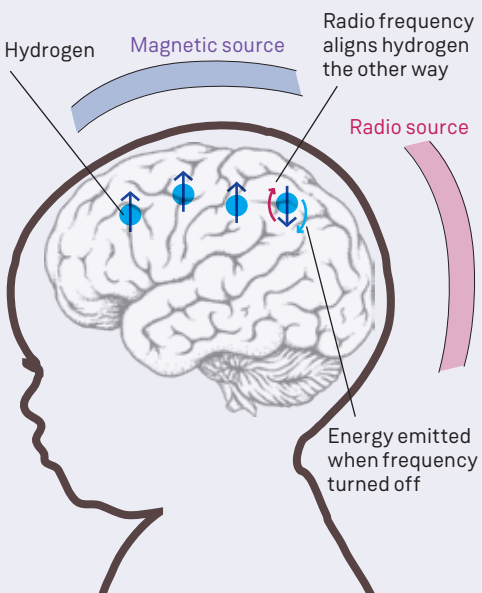


3

MAGNETIC RESONANCE IMAGING (MRI) AND SPECTROSCOPY (MRS)

MRI machines use strong magnets and radio frequencies to align and generate signals from hydrogen atoms in our body. MRS uses the same equipment but measures the concentration of specific chemicals rather than hydrogen. MRI and MRS are our gold standard for brain monitoring in babies.

MRI produces high resolution images used to identify the effects of brain injury. Measurements of specific chemicals from MRS inform us about future outcomes. In particular we use the ratios of two chemicals: lactate and N-acetylaspartate, as robust outcome biomarkers. These give us an understanding of metabolism and are the best way to predict outcomes.

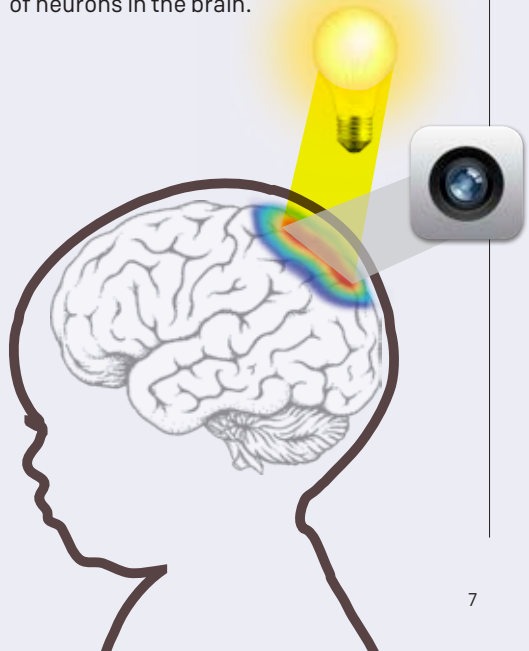


4

OPTICAL MONITORING

UCL remains the pioneering institution in using light-based technologies for new-born brain research. Recently, a new light-based technique – broadband Near-Infrared Spectroscopy (NIRS) – has shown significant promise in monitoring brain metabolism and blood flow, which is being trialled in the Neonatal Intensive Care Unit at University College London Hospital.
See more information in our Science issue.

Broadband NIRS uses optical markers to help babies with brain injuries. Early monitoring with broadband NIRS could allow early identification of which babies at risk of severe brain damage. These identified babies would benefit from additional treatments to provide optimal protection of neurons in the brain.



Developing biomarkers of brain injury in babies

by Gemma Bale, Medical Physicist and Dr Subhabrata Mitra, Consultant Neonatologist

CURRENT MEASUREMENTS

When a baby is being treated for brain injury the brain must be continuously monitored. Currently this is done using an electroencephalogram (EEG), but EEGs have practical limitations because they rely on specialised teams to set up the equipment and experienced doctors to read the results. Also, they detect only the electrical changes inside the brain.

CARING FOR BABIES AT UCLH

Doctors in the neonatal intensive care unit at UCLH are using CYRIL* (broadband NIRS technology developed by our MetaboLight team) to study newborn babies with brain injury and to find out more information about their injury. So far we've monitored the brains of over 80 babies at UCLH. Being able to monitor brain's oxygenation and metabolism (how oxygen is used) while the baby is undergoing treatment in intensive care can potentially offer huge benefits for doctors treating them.

*CYRIL = CYtochrome-c-oxidase Research Instrument and Application

FINDING METABOLIC MARKERS

More information about the brain oxygenation and metabolism of injured brains would help us better assess the damage and predict the severity of outcomes for the baby. Using broadband NIRS, we wanted to monitor the changes in cytochrome c oxidase concentration in brain which gives us an idea about how brain metabolism is affected by the injury.

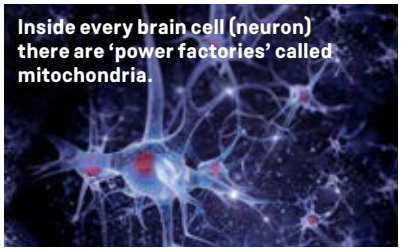
BABY BRAIN STUDY IN UCLH

It is important to identify the degree of brain injury at the cot side early on, so that doctors can decide the best treatments and make a difference to long term outcomes. Clinicians in our team have already developed a highly sensitive magnetic resonance spectroscopy (MRS) biomarker (based on the ratio of brain lactate to N-acetylaspartate) that can predict specific outcomes, but this can only be used in the MRI suite after a few days once the baby's cooling treatment has been completed. We wanted to develop a non-invasive biomarker using optical technologies that monitor continuous changes in brain metabolism at the cot side. Using broadband NIRS we could measure changes in concentration of cytochrome c oxidase, an enzyme within mitochondria that is responsible for most of the energy production within brain cells.

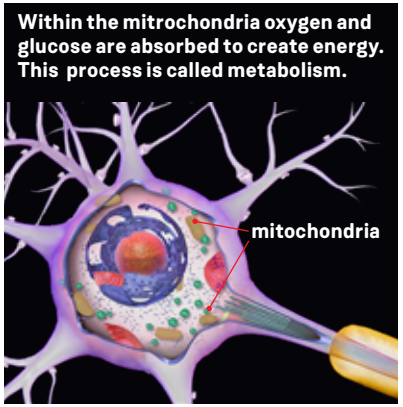
See more information in our Science issue.

We discovered that that we can predict the severity of brain injury and outcome by monitoring changes in cytochrome c oxidase. We investigated new-born babies with injured brains and found that the lactate to N-acetylaspartate values (measured by MRS) relate to changes in cytochrome c oxidase, changes in blood pressure, and neurodevelopmental outcomes. It was also clear that more severely injured brains had a different metabolic response (measured using cytochrome c oxidase) compared to babies who had less severe injury. We also identified how the two sides of the brain function differently after a brain injury, and demonstrated how brain blood oxygenation and metabolism changes quickly during seizures.

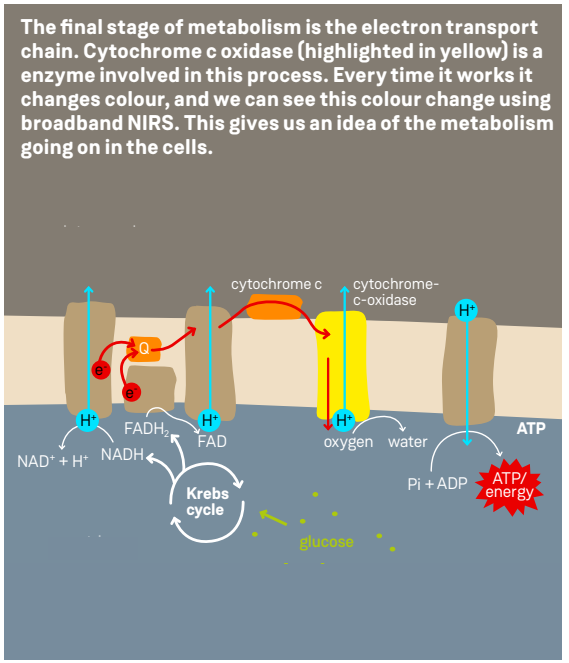
Our work has shown how this optical measurement of cytochrome c oxidase can show the activity of mitochondria after brain injury, resulting in different changes in brain metabolism. It appears to be a promising technology that could help clinicians detect and manage new-borns with brain injuries.



Inside every brain cell (neuron) there are 'power factories' called mitochondria.



Within the mitrochondria oxygen and glucose are absorbed to create energy. This process is called metabolism.



The final stage of metabolism is the electron transport chain. Cytochrome c oxidase (highlighted in yellow) is a enzyme involved in this process. Every time it works it changes colour, and we can see this colour change using broadband NIRS. This gives us an idea of the metabolism going on in the cells.

Working together to improve brain injury

Building on a long collaborative history between UCL and UCLH in developing technology to monitor newborns, our MetaboLight team of engineers, physicists and medical staff have developed broadband NIRS technology to help assess neonatal brain injury severity.

1980s

NIRS HISTORY

The history of optical technologies research for newborn brains goes back a long way, thanks to a strong collaboration between engineers, physicists and neonatologists at UCL and UCLH. Our diverse expertise led to pioneering publications and advances in this field, starting from a paper published in *The Lancet* in 1986.

2014

COLLABORATIVE TEAM

Working with a diverse team of engineers, physicists and doctors was key to our success in developing a novel broadband NIRS instrument called **CYRIL** that can measure metabolism and oxygenation in the brains of new-born babies. By working closely together our range of experts ensured the design was appropriate for hospital and patient use.

BROADBAND NIRS AT UCLH

Since 2014 broadband NIRS has been used in UCLH. Working closely with our medical partners at UCLH Neonatal Intensive Care Unit (NICU) enables us to integrate broadband NIRS at the cot-side together with standard monitoring equipment. Staff including nurses, radiographers and doctors has been crucial to setting up and conducting our studies in hospitals, helping us to evaluate NIRS technology.

2018

PUBLIC ENGAGEMENT

We have brought our pioneering engineering to the public through a carefully considered, multidisciplinary process of science and communication design, working alongside communication design team, Design Science. In July 2019 we are at the Royal Society Summer Science Exhibition.

The future

FAMILES AND PARENTS

Our systems use the latest technology and design to ensure babies' comfort. Families and parents are involved throughout the research and play a crucial part in developing broadband NIRS.

BROADBAND NIRS FOR ADVANCED NEUROMONITORING

Broadband NIRS monitoring has put us in a world leading position in neonatal brain monitoring in the neonatal intensive care. Studies have shown that monitoring metabolism using broadband NIRS techniques is important and has the potential to develop as an early cot-side, safe, non-invasive way of continuously assessing brain injury.

It can also support the development of new therapies and treatments. Although further testing is needed, we hope doctors in the future will have access these tools to give babies with brain injury the best chance in life at every NICU.

Shedding light on seizures

by Subhabrata Mitra, consultant neonatologist

Seizures are sudden rhythmic changes in brain electrical activity causing a temporary disruption to the brain's normal functioning. Because the newborn brain is rapidly developing and maturing, neonatal seizures are classed separately to seizures in older children and adults and can be difficult to identify.

WHAT CAUSES SEIZURES?

There are many causes of neonatal seizures. Common causes are **HIE**, **perinatal stroke**, **infections** and **hypoglycaemia (a drop in blood sugar)**, with HIE being the leading causes of seizures in newborn infants. Up to 75% of newborns with moderate and severe HIE can have seizures. A recent study found the rate of seizures in term infants in England was around 2 per 1000 live births.

WHAT DO SEIZURES MEAN FOR THE DEVELOPING BRAIN?

This is not entirely clear yet. But there is growing evidence that prolonged and recurrent seizures causes further damage to neurons (brain cells) and contribute to poor developmental outcome in babies.

CURRENT MONITORING TECHNIQUES

Seizures in newborns can be difficult to diagnose, which also means we might underestimate how many babies are truly affected by them.

- **Continuous video-EEG** monitoring of the electrical activity is currently the gold standard but a specialised team is needed to initiate and run the technology, as well as specialist doctors to report the findings. This technique is only available in a few specialised centres.
- **Amplitude integrated EEG (aEEG)** was developed to simplify the application and interpretation of this technology but has limitations for detection of seizures.
- **Video monitoring** can also help to identify any clinical changes associated with electrical changes noted on EEG.

WHAT CAN OUR OPTICAL MEASUREMENTS ADD TO THE PICTURE?

Broadband NIRS can be used to monitor changes in brain oxygenation, blood flow and metabolism during seizures. To detect oxygenation and blood flow, broadband NIRS detects changes in haemoglobin. Broadband NIRS also measures changes to CCO (an enzyme involved in respiration) which reflects changes in brain metabolism. Measurements of CCO are closely related to neuronal activity, so monitoring CCO during seizures can tell us how the brain uses energy.

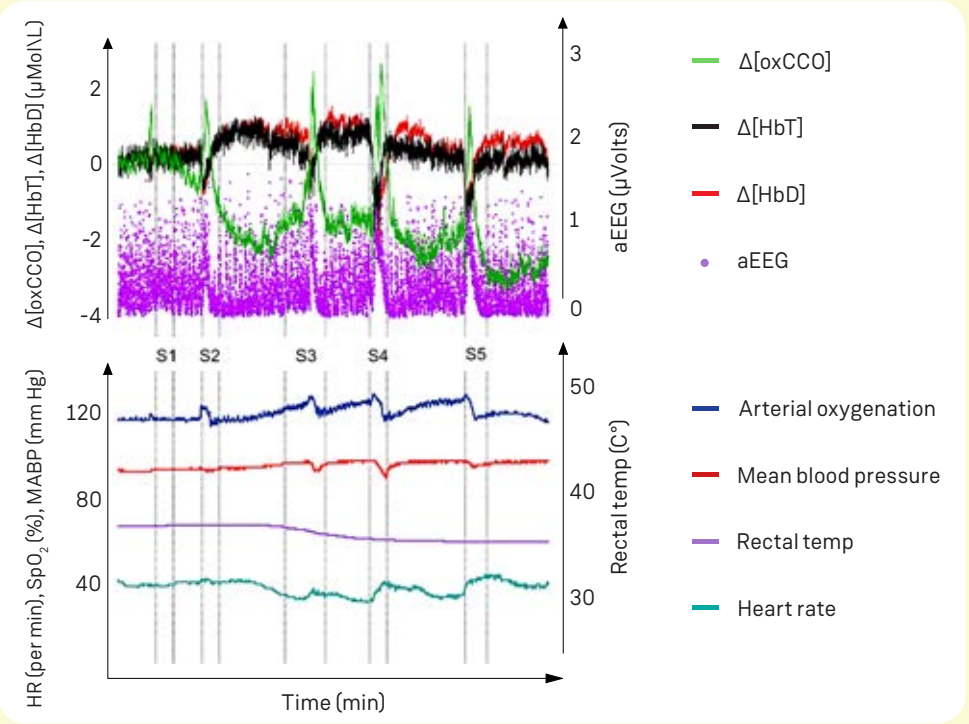
We used CYRIL (our broadband NIRS monitoring system) to monitor a newborn baby with moderate HIE who was having recurrent seizures.

First we collected different types/categories data simultaneously for a 90 minute period, including physiological measurements (such as heart rate and blood pressure) and aEEG recordings.

Looking at the NIRS and aEEG data, we found a rapid rise in CCO at the onset of seizures, which aligned with the aEEG changes. This suggested that neuronal activation and energy demand rapidly increased at the onset of seizures. After the peak of the seizure activity, we see a decrease in CCO levels, corresponding to a decrease in energy consumption. Most interestingly, we found that the baseline level of CCO dropped continually over time, with CCO levels decreasing towards and below the initial baseline values. This drop in CCO suggests that there is a progressive decrease of metabolism during repeated seizures, which might be why brain injury is often exacerbated after repeated seizures.

WHAT DOES THE FUTURE HAVE IN STORE?

We hope to use CYRIL in the future to monitor babies at the bedside and find out more about how seizures can affect the newborn brain. This could help us detect seizures earlier, manage brain health better, and shed light on the factors that lead to poorer health outcomes.



A day in the life: Subhabrata Mitra

We asked the **consultant neonatologist** and **MetaboLight team researcher** who looks after new-born babies at UCLH to tell us about his role

What do you do on a daily basis?
I look after small and sick new-born babies who need special support and care in the early period of their lives. Unfortunately, these babies are prone to developing brain injuries around the time of birth or in the first few days of life that can have significant impact for the rest of their lives. I have a research interest in perinatal brain injury and work as part of the UCL MetaboLight team in Medical Phsyics to develop systems that can identify vulnerable infants at an early stage, and to understand the background changes in brain physiology in these babies at the cot side using optical instruments. I spend much of my research time identifying infants for our study, talking to parents, running the study and finally analysing the data.

"We need to identify and intervene early and appropriately for infants that are prone to developing brain injury."

Who do you work with?
I work in a large multidisciplinary team. In the neonatal intensive care unit my team includes the medics and nurses along with specialists from different other important aspects of neonatal care (e.g., pharmacists, physiotherapists, psychotherapists). For research purposes I work with scientists, physicists, mathematicians and engineers from MetaboLight and UCLH. There is a long-standing history of collaboration between neonatologists in UCLH and the Medical Physics team for monitoring of new-born brain using light, and we have recently developed some unique purpose-built optical instruments which are being used for clinical research studies in the neonatal intensive care.

What are the highlights of your work?
The best part of my job is coming to hospital every day to work with the new-born babies! Babies can't tell you about their difficulties so we need to pick up all the subtle signs to understand their problems. Treating sick new-born infants in the intensive care and gradually getting them ready for discharge home is a journey that feels very rewarding. Often parents bring their babies back to the unit months or years after discharge. Seeing them doing well and getting older is always a fantastic feeling that keeps me going.

What are the toughest part of your work?
I enjoy my job, but it is hard when I need to sit down with parents and break bad news, particularly giving them information about their baby that will have adverse outcome for future.

What advice would you give for a junior?
Follow your dreams and enjoy the journey. If you are passionate and keep pushing yourself you will succeed.

What are your main ambitions?
To improve the cot side physiological monitoring for sick babies in the NICU using optical technologies. We need to identify and intervene early and appropriately for infants that are prone to developing brain injury. This will have a significant impact for their future outcome.

QUIZ

Metabolight crossword

Test your knowledge!

ACROSS

2 The age in months when baby's reflexes are coordinated

4 Within 90 days of birth the brain roughly doubles in _____

5 ____ NIRS uses optical markers to help babies with brain injuries

7 MRI stands for magnetic _____ imaging

11 MRI machines use strong magnets and radio ____

16 Brain monitoring technique that measures neuronal electrical activity

18 The parts of a cell that are responsible for its metabolism

19 The name of the broadband NIRS device used at UCLH in the neonatal intensive care unit

20 The most common form of brain injury (acronym)

21 MRS stands for magnetic resonance _______

DOWN

1 The age in months when a baby responds to stimuli

3 Brain monitoring technique that uses high frequency sound waves

6 The enzyme responsible for metabolism measured by broadband >'I.R.S (acronym)

8 The atom that generates the magnetic resonance signal in the brain

9 One of the symptoms of severe hypoxic ischemic encephalopathy

10 The type of doctor that provides medical care for new-born infants

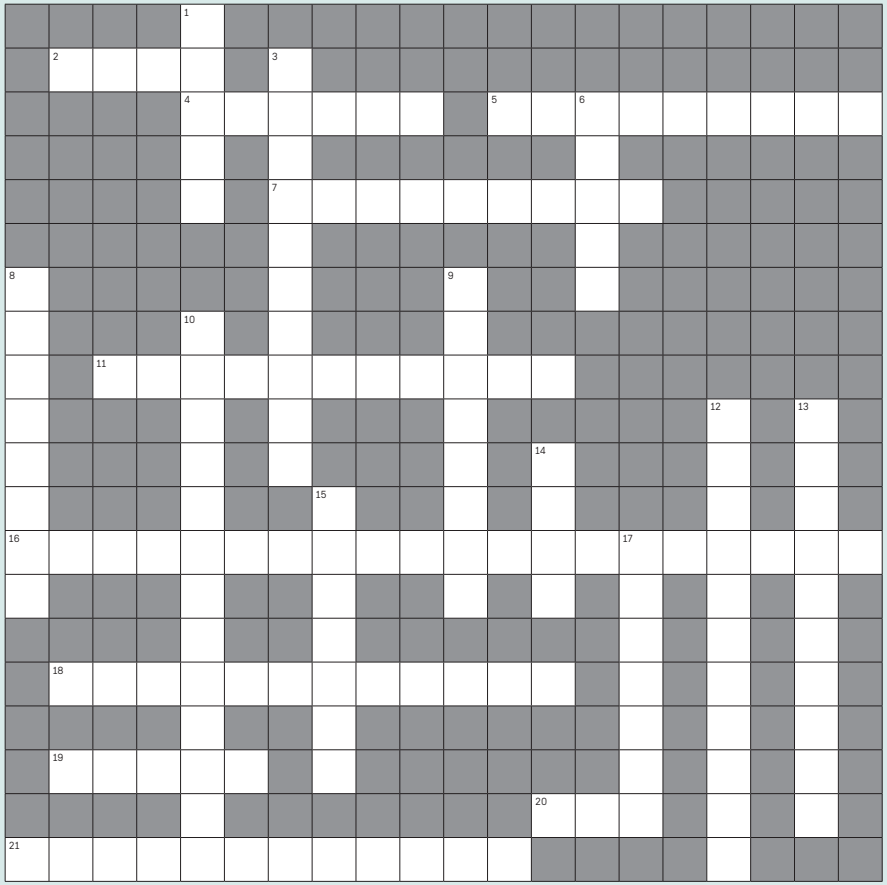
12 Broadband NIRS monitors the brain's _____ and metabolism

13 The production of energy in cells

14 The reflection of sounds waves measured in ultrasound imaging

15 The cells in the brain that carr ies the electrical impulses

17 One of the major biomarkers of metabolism identified by MRS



Answers available at: metabolight.org/resource/hospital-issue-answers

DIY SCIENCE

Measure your pulse

Try to measure your own heart rate with your phone

Courtesy to runtastic.com, azumio.com

HeartRate

HeartRateFree

1

Whether you are an Android or iPhone user there are numerous apps that allow you to measure your pulse. They make use of your camera and flashlight on the back of your phone and can measure your heart rate in a matter of seconds. But how do they do it? We can show you with these two free and easy to use apps.

2

Open the app. The flashlight of your phone should turn on. Try putting your finger onto it – the light from your phone will illuminate your finger into a bright red colour. This is because white light consists of all the colours of the rainbow but only red light can travel through our body. All the other colours are absorbed.

3

Cover your phone camera and flashlight with the same finger. The app should start detecting your heart rate and display it on the screen in "BPM", which stands for "Beats Per Minute". A healthy heart should have a heart rate of around 60 to 120 BPM.

4

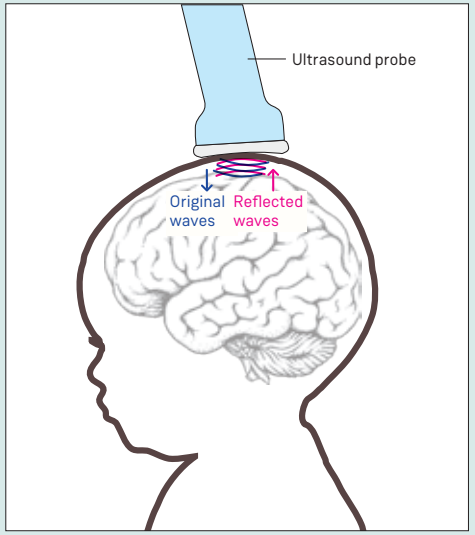
The science behind this is that when your heart pumps, blood pulses through your fingers and hence the amount of light that passes through your finger back into the camera changes. (Try not to move too much or the measurements may not be accurate.)

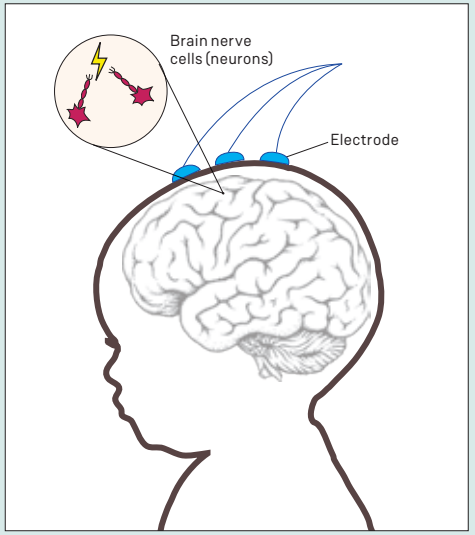
QUIZ

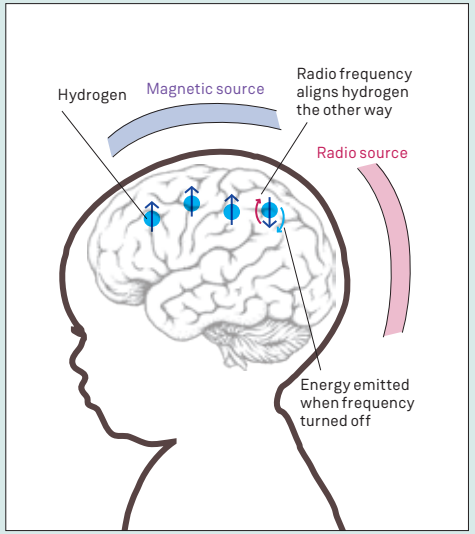
Match the modality

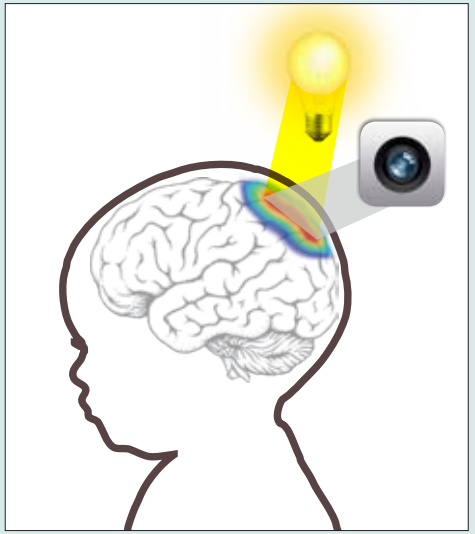
Match each image with the corresponding modality to monitor the brain of new-born babies.

Ultrasound imaging	MRI	Broadband NIRS	EEG









Answers available at: metabolight.org/resource/hospital-issue-answers

QUIZ SECTION

MetaboLight wordsearch

Can you find the following words? Words may be forward, backward, down or diagonal.

neonatologist
seizure
radio
hypoxic
frequency
cyril
severe
biomarker
probe
encephalopathy
ultrasound
magnetic
lactate
ischemic
broadband
infrared
brain
mitochondria
oxygenated
resonance
monitoring
neonatal

D	M	Z	D	C	P	S	E	M	O	T	D	S	J	U	J	H	C	O	Y	T	Y	S	R	K	C
O	A	L	S	R	W	Z	Z	S	P	Q	X	J	Y	I	V	A	O	X	P	D	X	Q	N	G	B
N	T	E	P	Y	I	E	L	P	H	B	V	E	A	I	Z	Z	V	D	Q	B	S	I	W	K	S
X	T	B	M	Y	B	O	D	B	Y	K	T	I	K	Q	A	G	Y	U	C	L	A	F	V	O	G
J	N	G	M	L	V	B	P	M	H	C	M	E	B	O	R	P	Y	E	O	R	W	W	Y	F	D
V	W	Z	V	F	S	A	U	B	Q	G	C	I	J	I	S	N	V	J	B	X	T	W	Q	P	O
S	O	X	P	S	R	D	N	U	O	S	A	R	T	L	U	R	K	M	G	L	T	F	U	C	O
Z	B	F	R	E	Q	U	E	N	C	Y	V	W	T	O	R	N	E	S	U	C	D	H	W	N	P
T	R	R	Z	U	H	J	L	D	U	G	G	C	K	A	C	H	Y	P	O	X	I	C	R	Z	X
N	L	S	E	D	E	H	K	N	V	G	X	C	J	Q	A	H	P	J	K	W	C	P	A	E	N
Y	E	C	B	K	Y	D	O	A	M	V	R	Y	H	T	A	P	O	L	A	H	P	E	C	N	E
H	X	O	U	Y	R	I	T	B	V	H	W	V	Z	T	H	A	U	N	B	H	D	P	W	K	M
Z	P	Z	N	Y	D	A	M	D	J	D	E	R	A	R	F	N	I	C	D	A	G	I	W	B	G
K	F	R	A	A	P	K	M	A	U	V	P	M	W	N	U	F	W	W	H	R	O	J	S	X	K
T	M	W	R	I	T	M	J	O	G	A	U	E	B	Y	E	Y	B	G	O	L	I	N	H	S	V
O	O	K	R	C	R	O	R	R	I	N	B	T	A	V	A	U	I	P	W	I	A	I	D	Z	N
S	N	C	Q	R	N	S	L	B	Q	B	E	A	A	Q	P	B	Q	U	J	Q	O	S	Q	D	W
N	I	E	T	P	I	E	F	O	D	Q	E	T	A	Y	V	K	I	H	W	W	C	D	E	B	T
H	T	I	C	O	J	C	O	B	G	H	U	C	I	Q	L	I	L	N	K	H	O	T	X	Z	K
K	O	B	X	N	R	I	D	N	E	I	B	A	Y	C	E	R	E	V	E	S	A	W	A	I	J
L	R	J	N	M	A	X	J	R	A	W	S	L	V	Y	J	L	I	M	K	N	X	W	S	N	A
J	I	F	X	I	E	N	U	T	J	T	A	T	P	R	D	L	I	Z	E	Y	L	K	O	Y	K
S	N	H	M	J	N	Z	O	Y	W	Z	A	G	Y	I	B	C	Y	G	E	P	U	N	C	A	X
B	G	O	X	U	I	V	P	S	M	B	K	L	Q	L	T	Z	Y	O	M	V	M	Z	L	R	F
H	B	P	R	E	S	S	C	A	E	V	D	F	W	H	K	X	H	F	M	V	T	U	Z	D	T
F	J	I	S	P	T	T	E	F	B	R	K	U	S	M	O	T	K	N	U	W	E	B	Z	X	A