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Neurological Products

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NB please note that some of the following slides vary slightly from those used at the Investor Day on the 12th May due to the reformatting of some of the animated slides.

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Neurological Products

Renishaw is applying precision engineering technology to the challenges of functional neurosurgery.

Our aim is to help leading clinicians to enhance the safety and cost-effectiveness of their procedures, improving patient outcomes through accurate delivery of implantable devices.

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Our target market

Our target market is Neurosurgical Centres. Specifically centres specialising in stereotactic neurosurgery (the delivery of instruments and/or devices accurately and repeatability into the brain)

These units require;

- **High accuracy** – specific placement of devices and instruments into the brain
- **High effectiveness** - low opportunity for error, improved patient outcomes
- **High efficiency** – health economic. More procedures, more revenue

Examples of Neurosurgical procedures

- **DBS** - Deep Brain Stimulation
  - Accurate placement of electrodes into small structures of the brain
  - Typically for treating the symptoms of movement disorders such as Parkinson's disease
- **SEEG** – Stereoelectroencephalography
  - Diagnostic procedure for Epilepsy
  - Replaces the need for craniotomies and the use of subdural grids associated with increased infection rates
  - Typically placing 12 to 17 electrodes
- **Stereotactic Biopsy**
  - Accurate removal of tumour sample for analysis
  - Minimise damage during procedure
- **Intraparenchymal drug delivery**
  - Delivery of drugs directly into the brain to circumvent the blood-brain barrier

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Engineering solutions – a systems approach

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neuro I mate® stereotactic robot

- The first image-guided neurosurgical robot in the world
- Used in over 10,000 neurosurgical procedures
- More than 30 scientific peer-reviewed publications
- CE marked & cleared for sale in the USA
- In use in leading neurosurgical centres in France, UK, Italy, Germany, Peru, Qatar, KSA and the US

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Improved precision and increased speed*

Precision		Average	Range
DBS[2]	Frame	1.03 mm	0.62 mm - 1.44 mm
	Robot	0.81 mm	0.33 mm - 1.29 mm
SEEG[1]	Frame	1.43 mm	0.91 mm - 2.21 mm
	Robot	0.78 mm	0.49 mm - 1.08 mm
Speed		**Average**	**Range**
DBS[2]	Frame	55 min	+/- 17 min
	Robot	23 min	+/-13 min

*Compared to other stereotactic systems

1) Cardinale et al, Neurosurgery 72:353–366, 2013
2) Barua et al, Stereotactic Functional Neurosurgery 2013;91(suppl. 1): 1-334-Page 102

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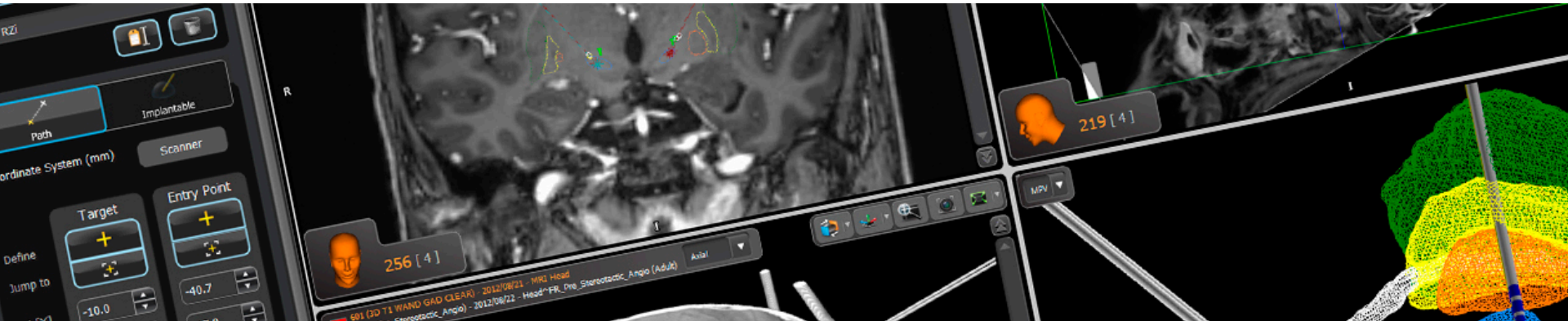
neuro I inspire™ surgical planning platform

- Rapid, accurate planning of stereotactic surgeries
- Multi-planar image reconstruction
- Brain atlas to provide reference features during planning
- Intuitive planning process
- Detailed modelling of implanted devices
- Manual anatomy segmentation



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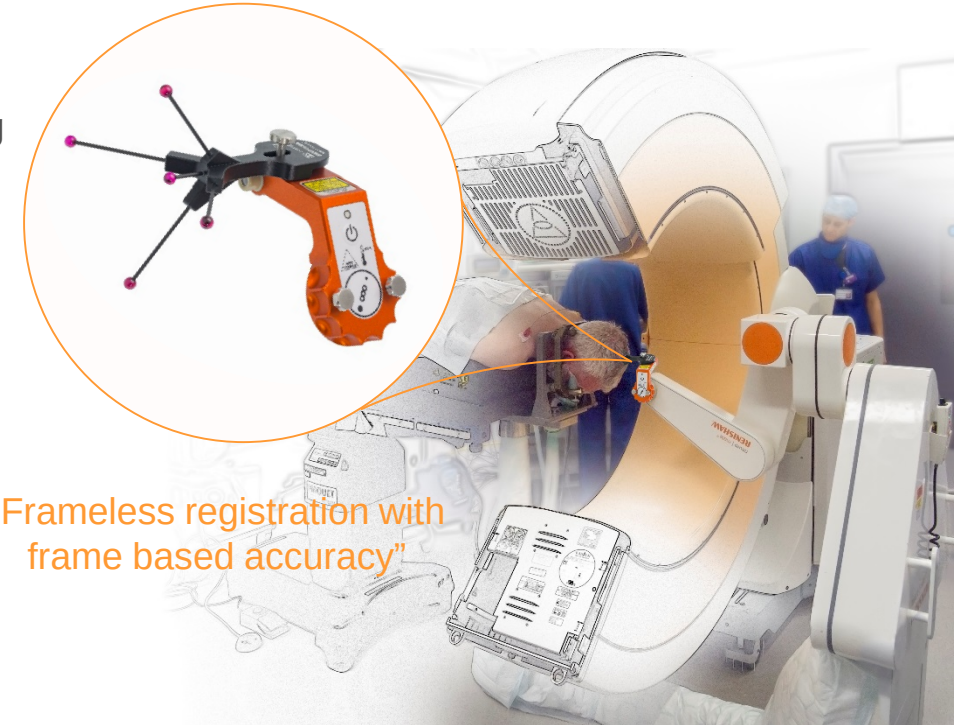
neuro | locate™ - advanced patient registration system

***neurolocate*™ is a new frameless patient registration module for use with the Renishaw *neuromate*® stereotactic robot.**

- Potential for time and cost saving by utilising the benefits of intraoperative imaging in the operating room;
- Improved patient comfort due to shorter procedure times and absence of bone or skin anchored fiducials;
- Increased flexibility of the patient head position due to the adjustable nature of the fiducial marker frame;
- Compatible with existing frame systems for holding the patient head on the neuromate.



"Frameless registration with frame based accuracy"

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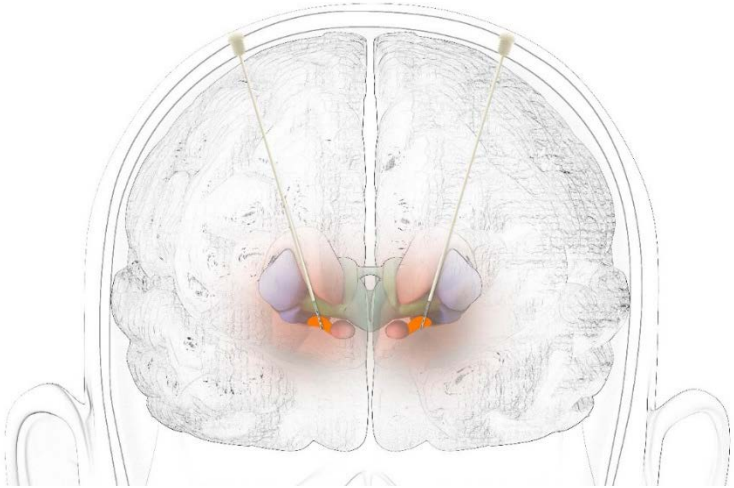
neuro | guide™ DBS electrode delivery system

- Allows verification of expected DBS lead position relative to targeted anatomy using MRI data
- **Guide tube**: permanent implant secured to the skull that acts as electrode conduit
- **Stylette:** temporary implant for peri-operative MRI/CT confirmation



Consumables and tooling – DIXI medical

- Renishaw is an exclusive distributor for DIXI medical in UK & Ireland;
- DIXI are a manufacturer of specialist electrodes and instruments for use in stereotactic neurosurgery;
- Such as;
  - depth electrodes
  - biopsy needles
  - cortical grids
  - accessories

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Drug delivery – support for Clinician led study

- Manufacturing an investigational intraparenchymal drug delivery system for an NHS Trust provider
- Clinician-led Phase II trial under way to deliver a drug for the treatment of Parkinson’s disease
- This system has also been used by the Trust for delivery of a chemotherapy drug for the treatment of brain tumours

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Successful outcomes - Epilepsy

- Stella (aged 13) developed severe epilepsy when she was 1 year old and subsequently endured up to 100 life threatening seizures every day.
- Over 10 years, she underwent 5 invasive surgical procedures, and after every procedure, the seizures returned immediately, often more violently.

Traditional method: electrocorticography (subdural grids)

Successful outcomes - Epilepsy

- Their last hope was at the Niguarda Ca' Granda hospital in Milan, Italy where the neurosurgical team are pioneering the use of the Renishaw *neuromate*® stereotactic robot for the treatment of epilepsy (SEEG).

- Due to the precision and stability of the *neuromate* robot, they were able to reach parts deep in the brain that were not accessible through other methods, thus enabling them to identify the exact location of the brain that triggered her seizures. The identified section was then removed.
- Immediately after surgery, Stella's seizures stopped and the family have a whole new life ahead of them.

Alternative method: Stereoelectroencephalography (SEEG)

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Clinical – The Bristol/Renishaw collaboration

Targeted drug delivery to the brain
What is the potential?

Mr Neil Barua PhD, FRCS(SN)
Department of Neurosurgery
Southmead Hospital
Bristol

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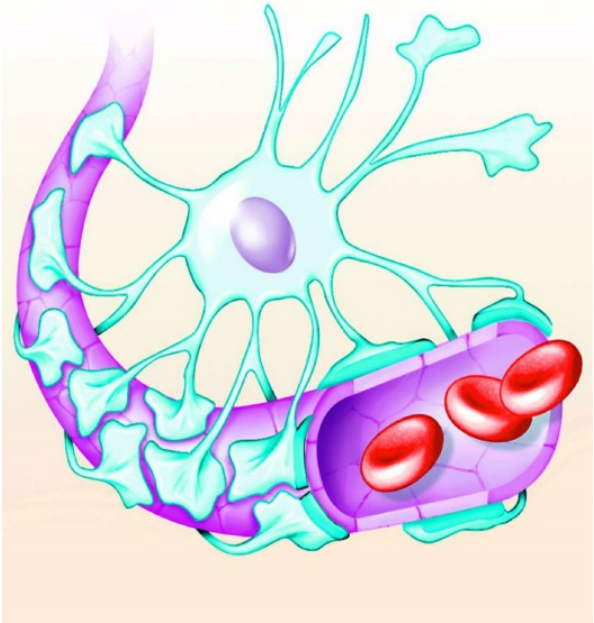
Drug delivery to the brain – what is the challenge?

- **The blood brain barrier (BBB) – nature's defence mechanism**
  - Prevents transfer of drugs from the bloodstream into the brain
  - The BBB is considered to be the single most important limiting factor in developing effective therapies for neurological disorders
  - Implicated in poor response of brain tumours to chemotherapy



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Drug delivery to the brain – what is the solution?

- **Convection-enhanced drug delivery**
  - Direct delivery of drugs into the brain
  - Highly accurate placement of microcatheters into the brain
  - Controlled infusion of drugs
  - Distribution of infusate through large brain volumes

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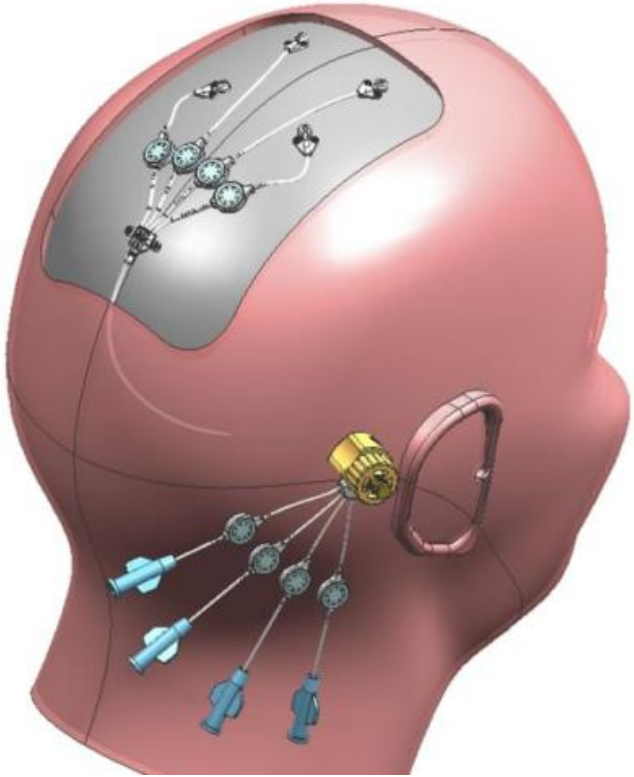
The solution – an implantable catheter system



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Direct drug delivery to the brain

The Bristol/Renishaw Experience

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The surgical process – pre-operative MRI scanning

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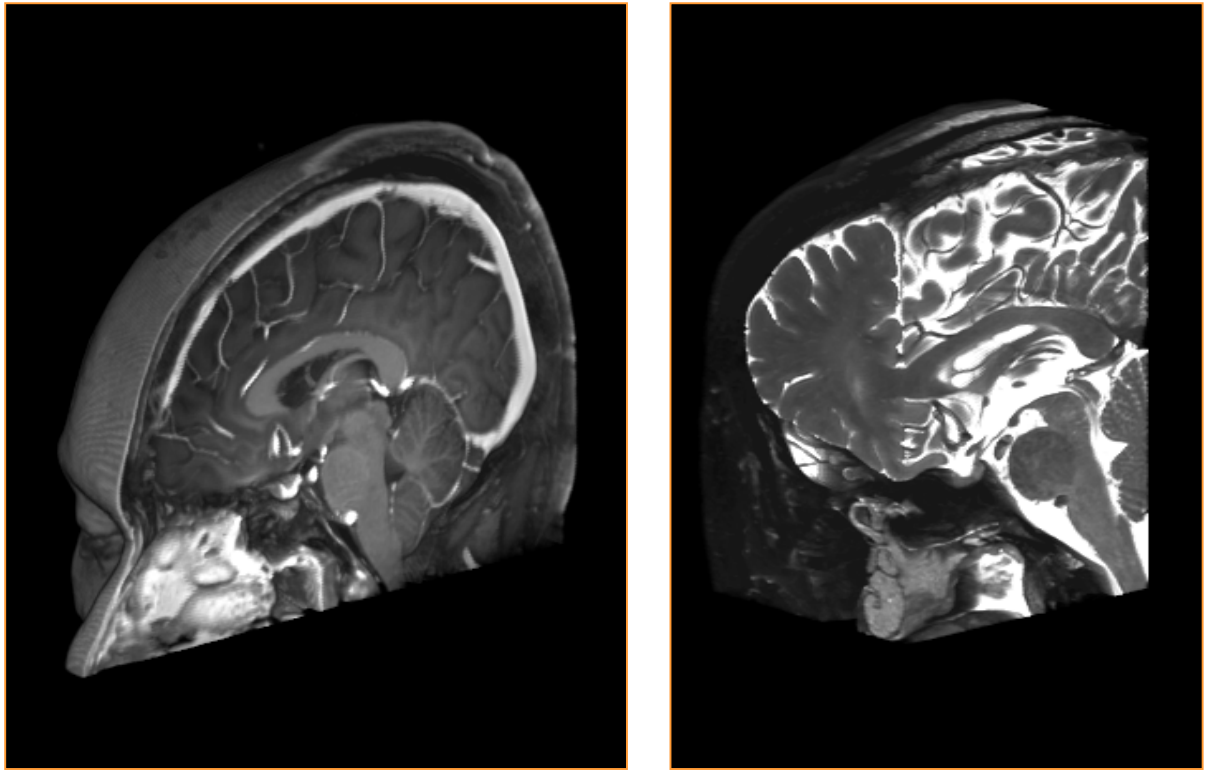
neuroinspire – surgical planning software



Source: Renishaw *neuroinspire* software

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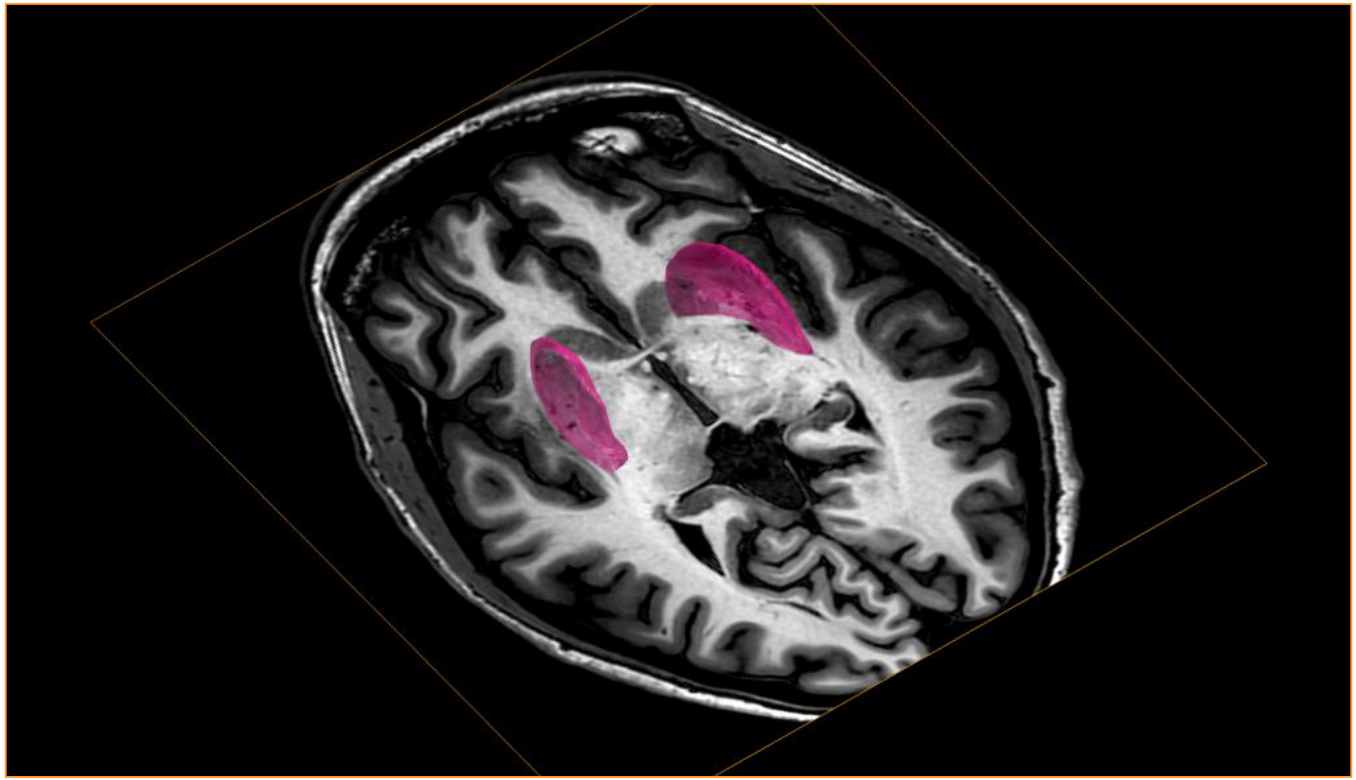
Automatic identification of brain structures



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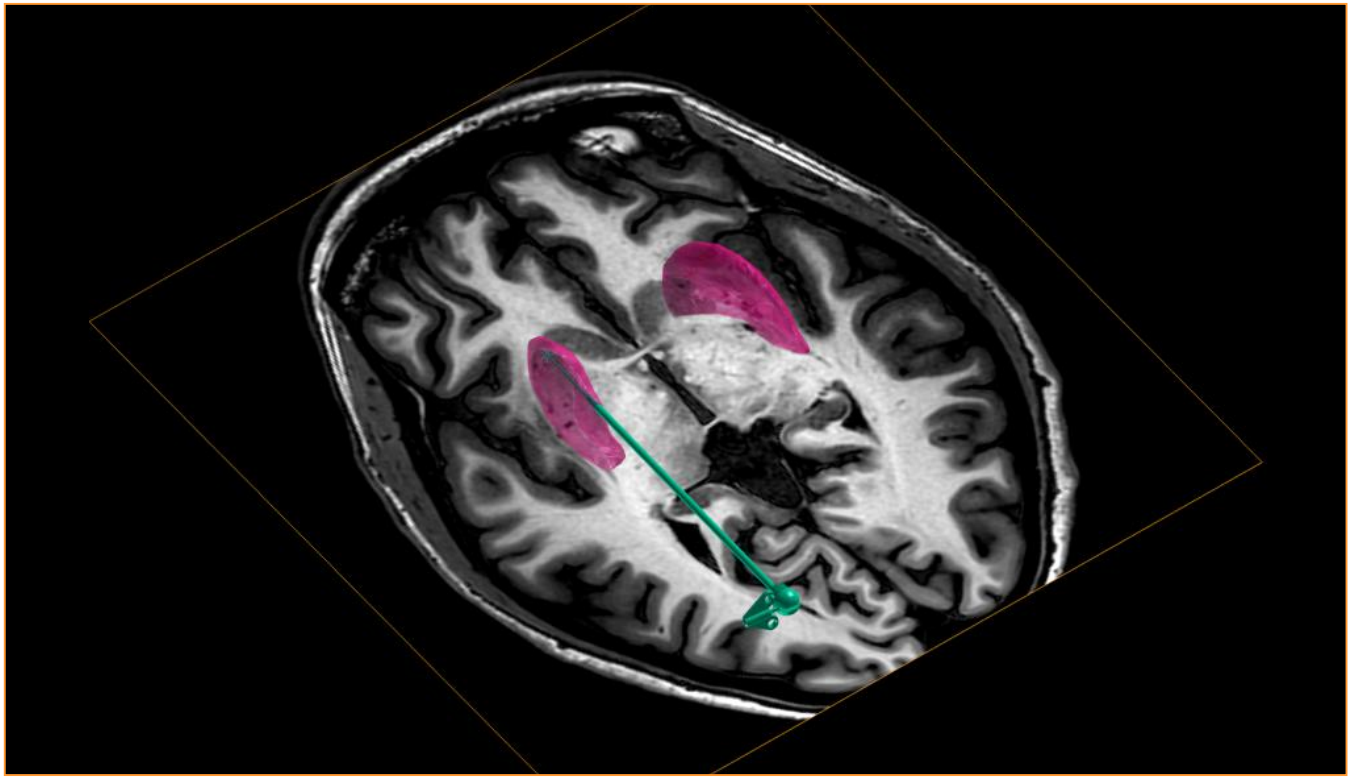
Trajectory Planning



Source: Renishaw *neuroinspire* software

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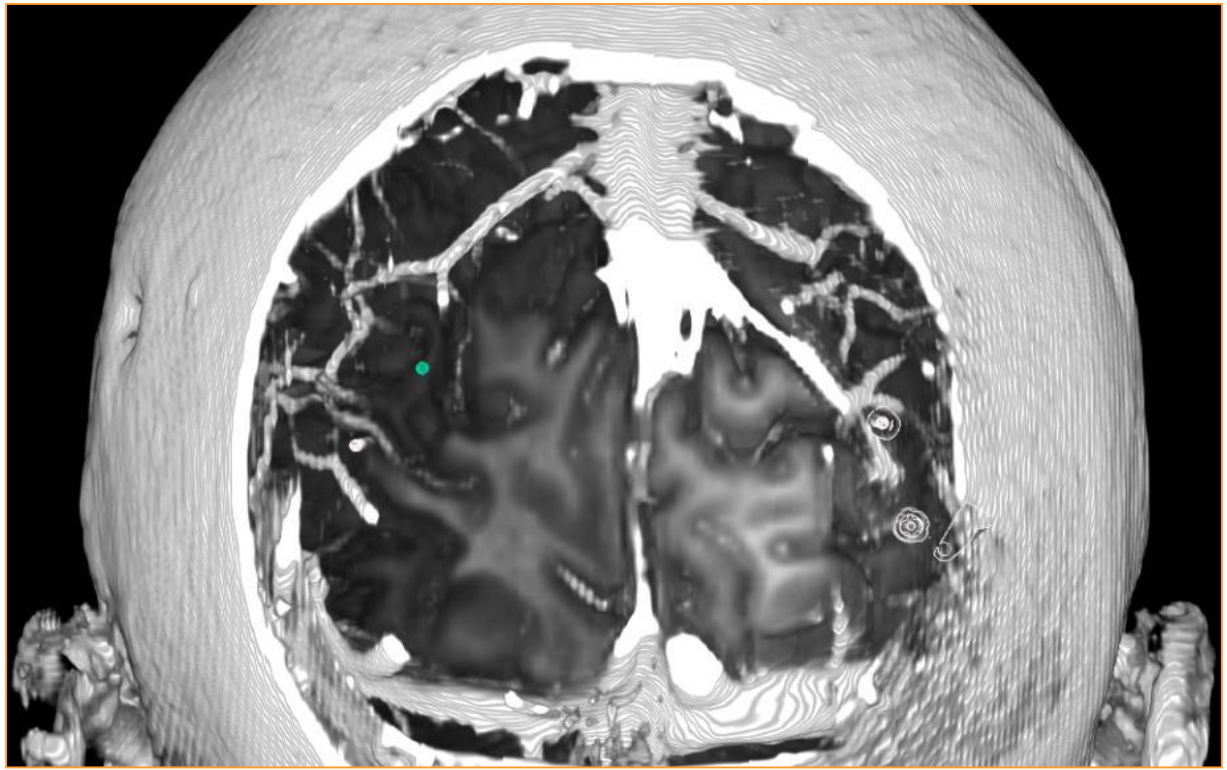
Safe surgical trajectories



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neuromate – Robot assisted surgery

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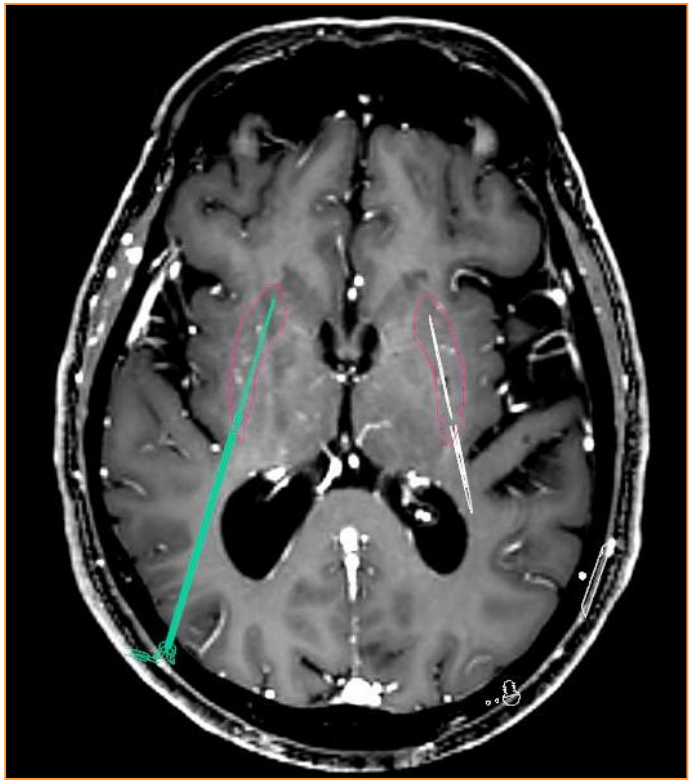

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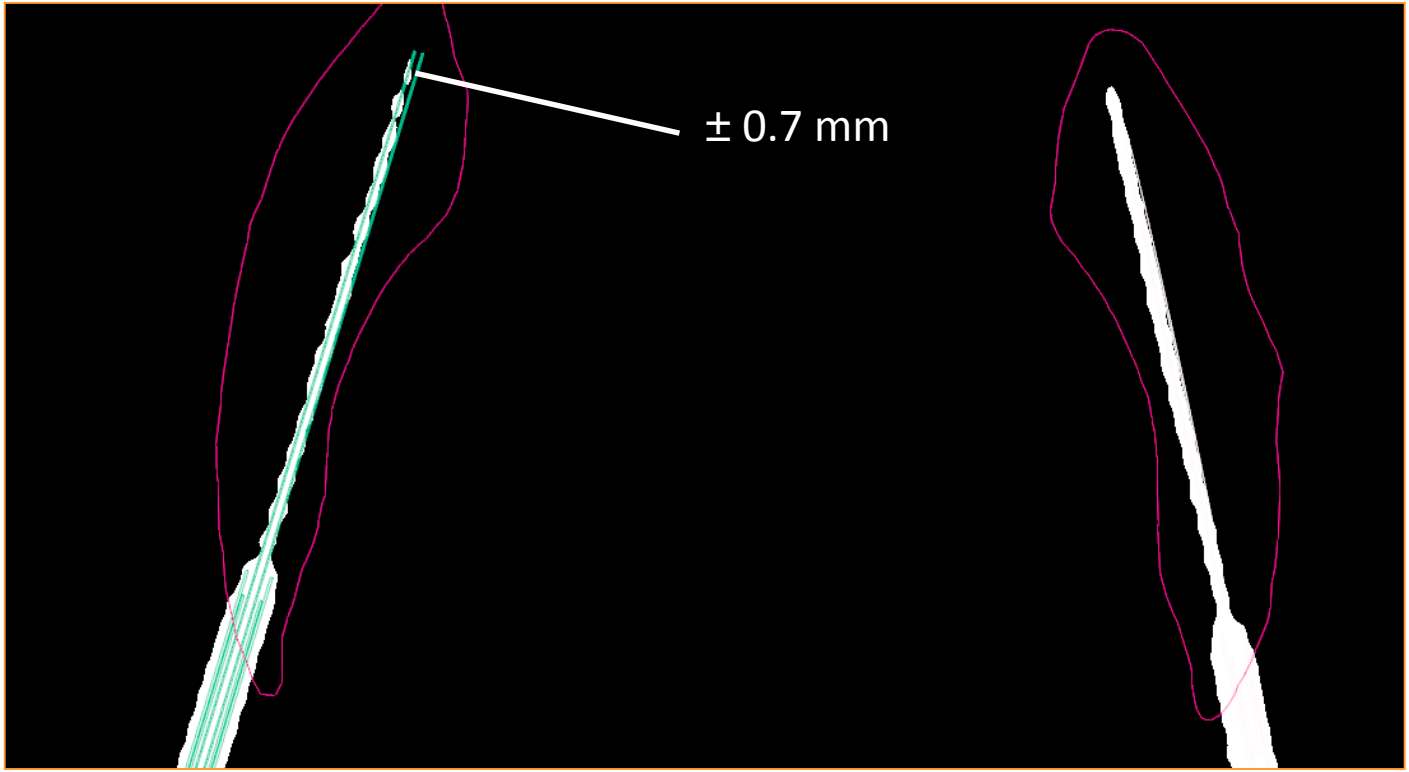
Accuracy of catheter placement



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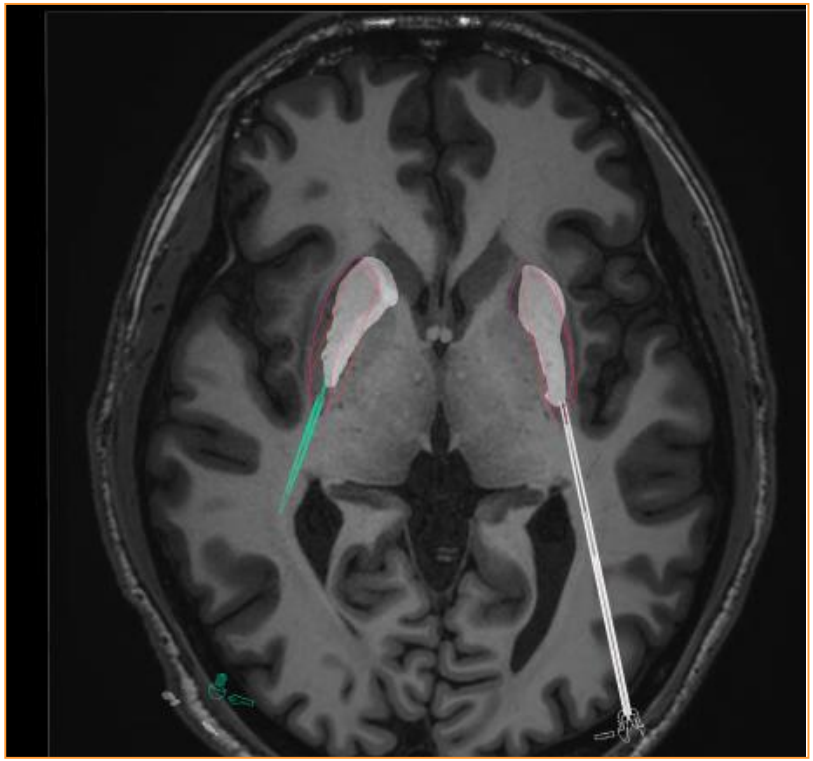
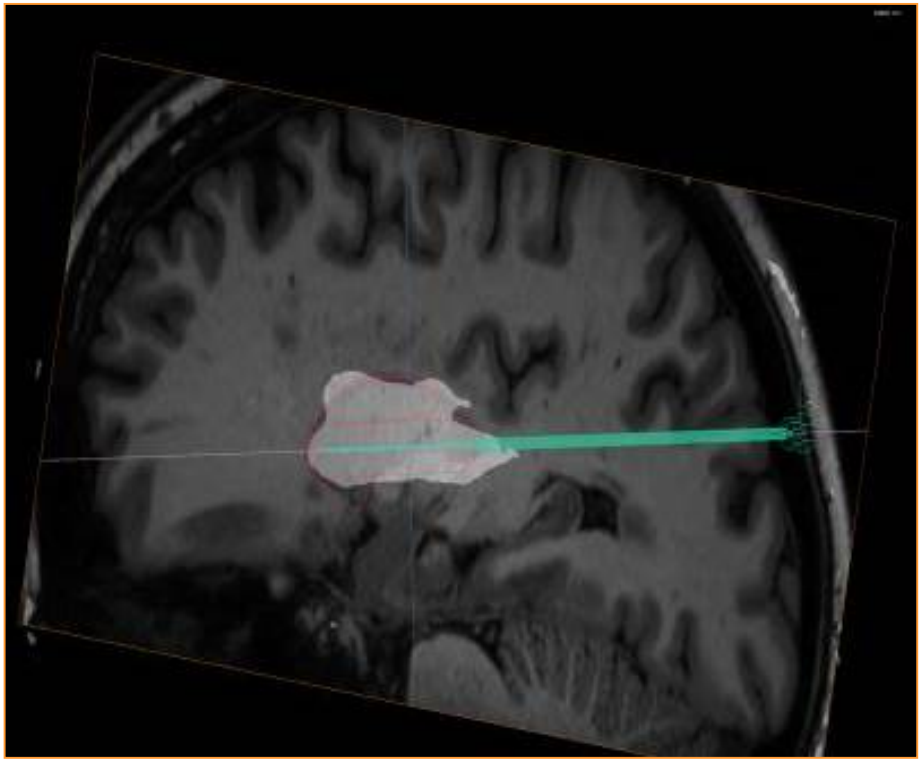
Infusion of a test agent





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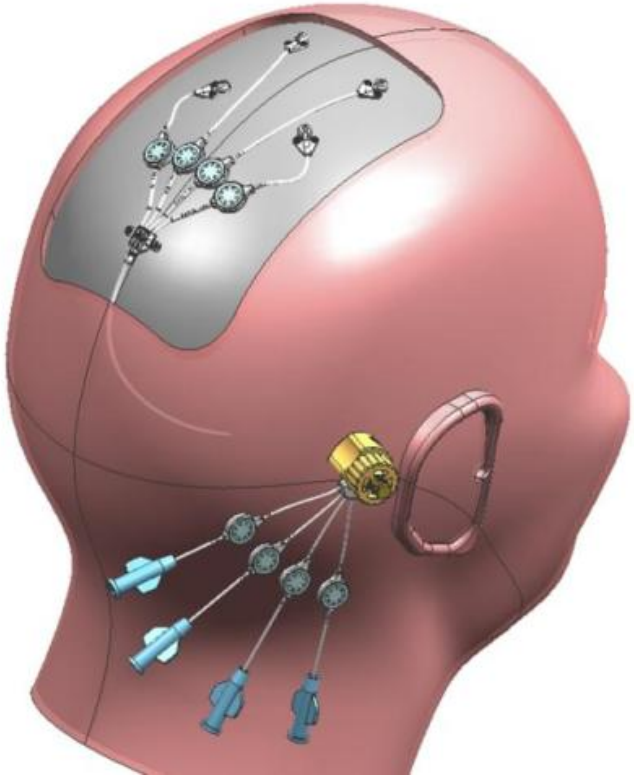
Repeated drug administration



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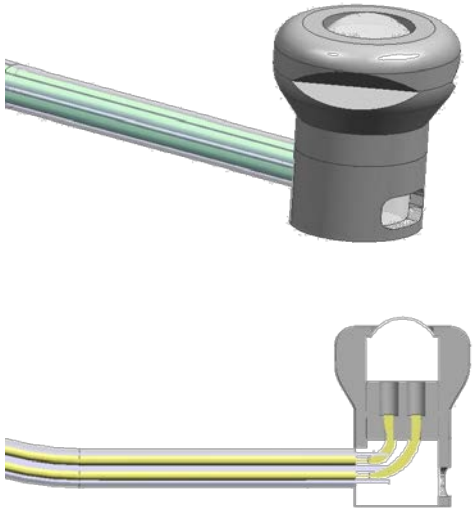
Transcutaneous bone-anchored port



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Attachment of administration set

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Treatment of brain tumours with chemotherapy infusions

- 4 adults with progressive/recurrent glioblastoma – average survival less than 1 year

- 11 children with brainstem glioma – average survival 7 to 9 months

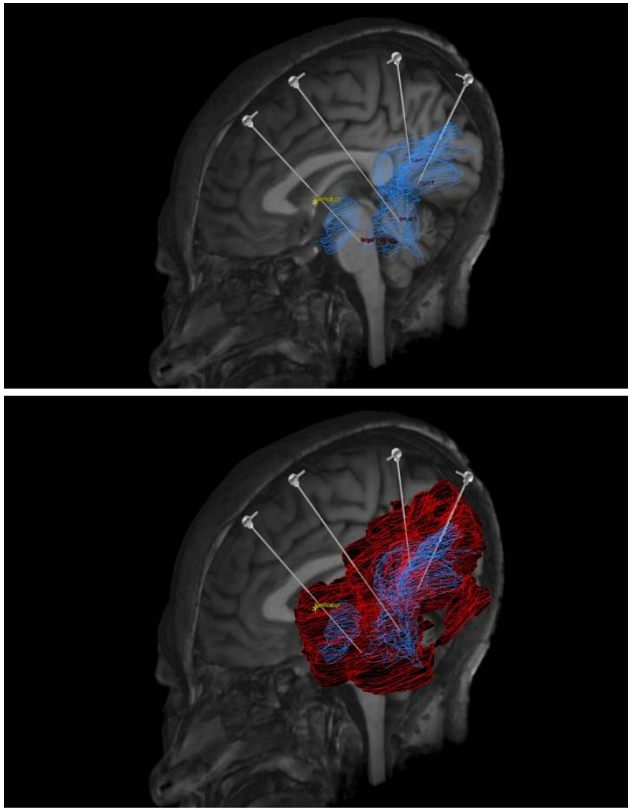
- 1st patient

- 52 years old

- Recurrent glioblastoma

- 2 previous surgeries

- Radiotherapy & chemotherapy



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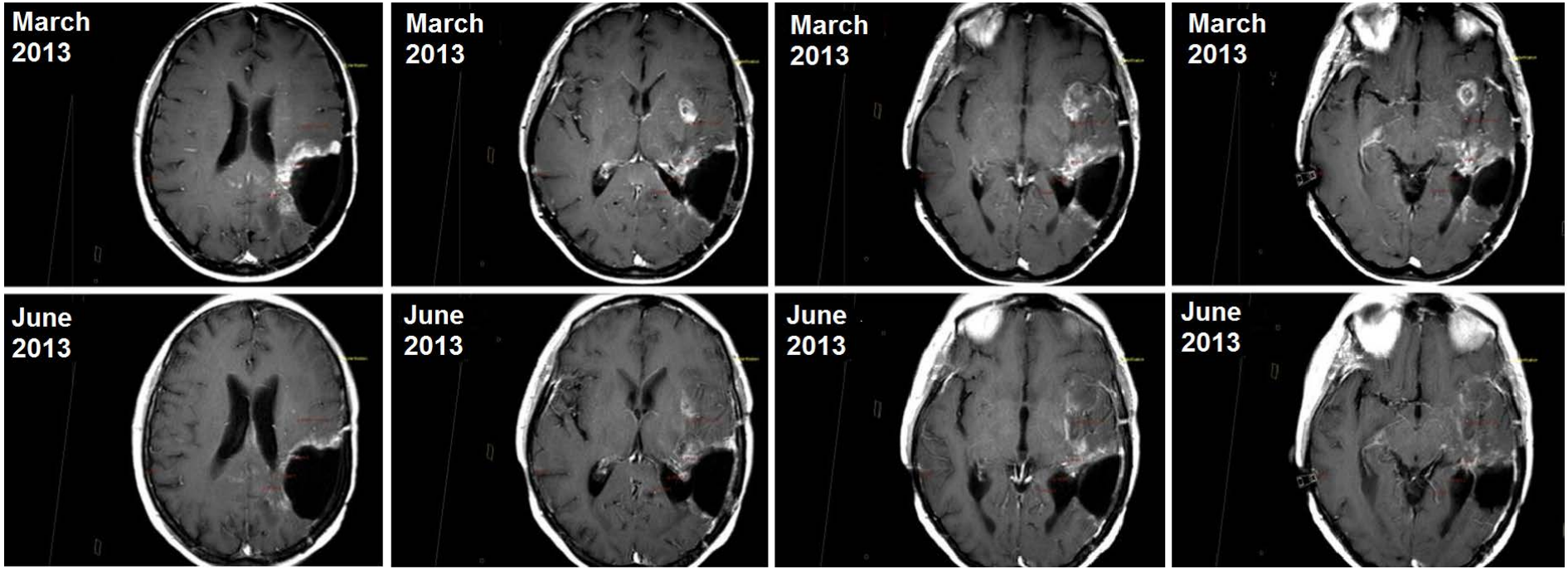

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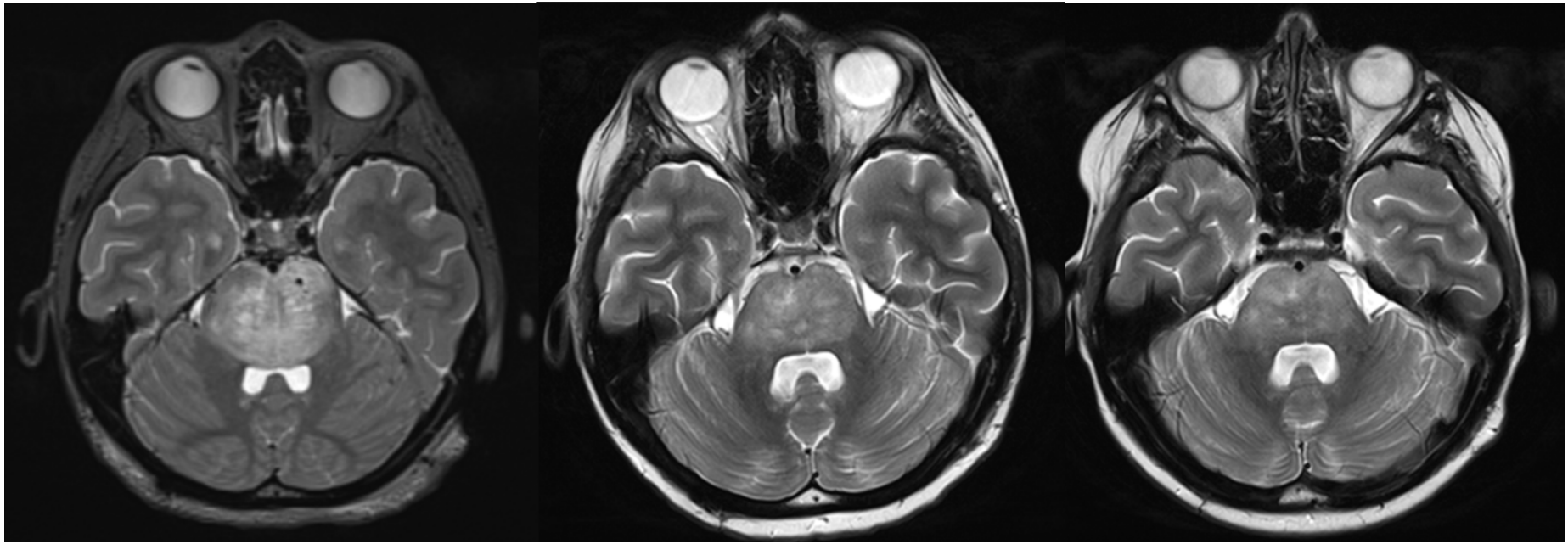
12 year old boy with brainstem tumour

Dec 2014 | Jan 2015 | March 2015



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Direct drug delivery to the brain – what is the potential?

- Largest experience worldwide of repeated drug infusions
- Application to a wide range of neurological diseases – Parkinson's Disease, brain tumours, Alzheimer's Disease…
- Unique and world-leading technology
- Technology allows delivery of proteins, chemotherapies, nanoparticles, gene therapies…
- May open the door to curative treatments

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Renishaw Healthcare Centre of Excellence

- Training is an important part of product development and beyond
- Familiar operating environment will ensure realistic conditions/feedback
- Brings manufacturing process expertise to the Operating theatre
- State-of-the-art training facility includes;
  - Fully functioning (non-sterile) operating environment
  - X-ray proofed room with CT scanner
  - Remote training capabilities
  - Recording/playback facilities
  - Preparation room and changing room

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Thank you