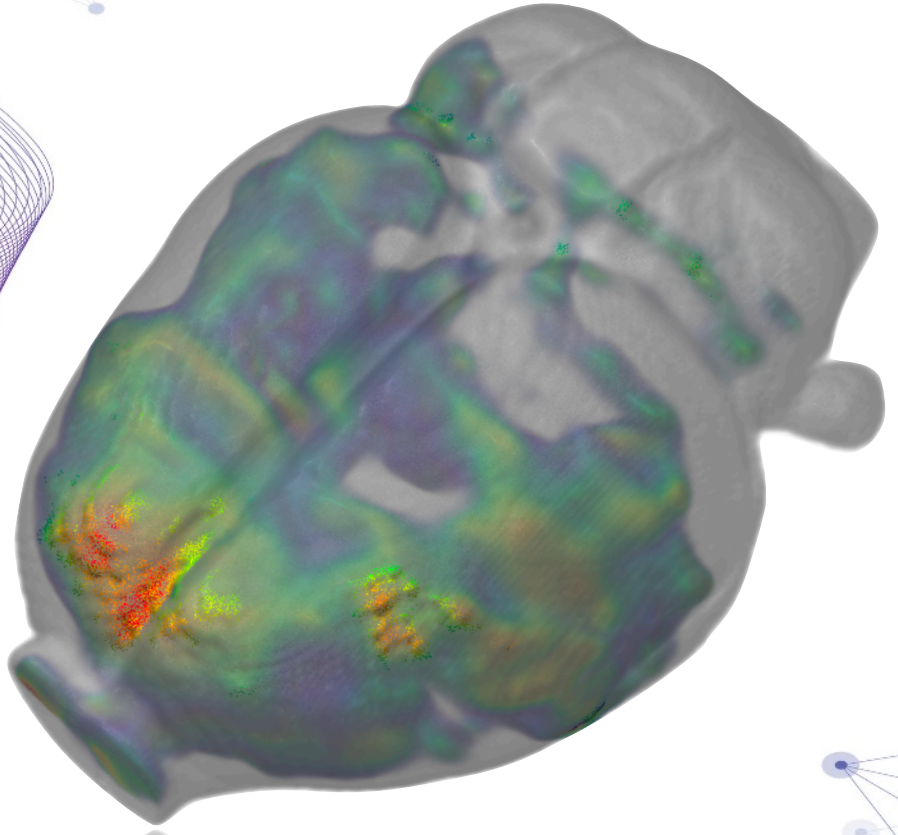
Pre-Clinical Functional Neuroimaging: Techniques for Comprehensive Characterisation of Drug Effect in the Brain



L&M DATA SCIENCE

CONTENT

Navigating Excellence: Precision in Pre-Clinical Neuroimaging with L&M Data Science

Decrease time for results

Increse confidence

Increse translational value

Welcome to the forefront of pre-clinical neuroimaging innovation. In the world of pharmaceutical research, where every new insight can change how we develop treatments, being precise and reliable is incredibly important. At L&M Data Science, we're here to help you improve your drug development programme with our pre-clinical neuroimaging services.

We're not just about offering solutions; we're dedicated to understanding the complexities of the central nervous system. In this brochure, we invite you to explore our approach, which includes using the latest techniques, focusing on stable physiology, and combining complementary methods for better results. Through these approaches, we provide more than just a service; we offer you a quicker path to make new discoveries and make well-informed decisions as you work on advancing treatments for neurological and psychiatric conditions.

With our high-throughput platform, **neuroPhINDr** (neuroimaging for pharmacological identification of novel drugs), we speed up the time it takes to get results by making our processes more efficient, boosting confidence by ensuring our results can be replicated, and increasing the translational value of our work by using the same techniques used in human patients. These commitments and our accuracy, innovative methods, and ethical research practices give you the tools to make intelligent decisions and drive progress in the ever-evolving neurological and psychiatric treatment field.

As you read the pages ahead, you'll see we're all about quality, precision, and maintaining the highest scientific standards. Join us in changing the way pre-clinical neuroimaging is used in pharmaceutical research. Your journey towards innovation starts right here with L&M Data Science.

Dr Michel Mesquita, CEO
L&M Data Science

Challenges in Neurological and Psychiatric Treatment Development

- Neural Interactions
- Disease Modeling
- BBB Penetration
- Efficacy Evaluation
- Safety
- Long Timelines
- Inter-Species Variability
- Ethics

Pharmaceutical companies face complex challenges in the early stages of developing drugs for neurological and psychiatric conditions. These include understanding intricate neural interactions, creating accurate disease models, overcoming the blood-brain barrier, objectively assessing efficacy, ensuring neurological safety, managing long experimentation timelines, addressing differences in how animals and humans respond and navigating ethical considerations related to animal and human research. To conquer these obstacles, extensive research, collaborations, technological advancements, and innovative approaches are needed. At L&M Data Science, we understand the complexities of drug development and offer cutting-edge solutions to help our clients achieve their objectives.

Taking On These Challenges With Complementary Techniques

L&M Data Science employs a sophisticated trio of techniques to gain profound insights into the complexities of the central nervous system: BOLD fMRI, arterial spin labelling (ASL), and EEG. Together, these methods provide a multifaceted perspective on neural activity, connectivity, and dynamics, effectively painting a vivid and comprehensive picture of how the brain responds to experimental interventions.

BOLD fMRI: Mapping Functional Activity

At the heart of our approach is Blood Oxygenation Level Dependent fMRI. This technique allows us to visualise changes in blood flow and oxygenation in the brain. It's like creating a detailed map of functional brain activity, highlighting which regions activate or deactivate during specific tasks or under certain experimental conditions. By doing so, we gain spatial insights into how different parts of the brain collaborate and respond to the effects of drugs.

Arterial Spin Labelling (ASL): Quantifying Blood Flow

ASL plays a crucial complementary role by directly measuring cerebral blood flow. Through magnetic labelling of arterial blood, ASL enables us to observe changes in blood perfusion, shedding light on tissue metabolic demands and local hemodynamics. This method provides valuable information about how experimental drugs influence blood flow in different brain regions, adding depth to our understanding of drug effects on the brain.

3 x the Data in 1/3 of the Time

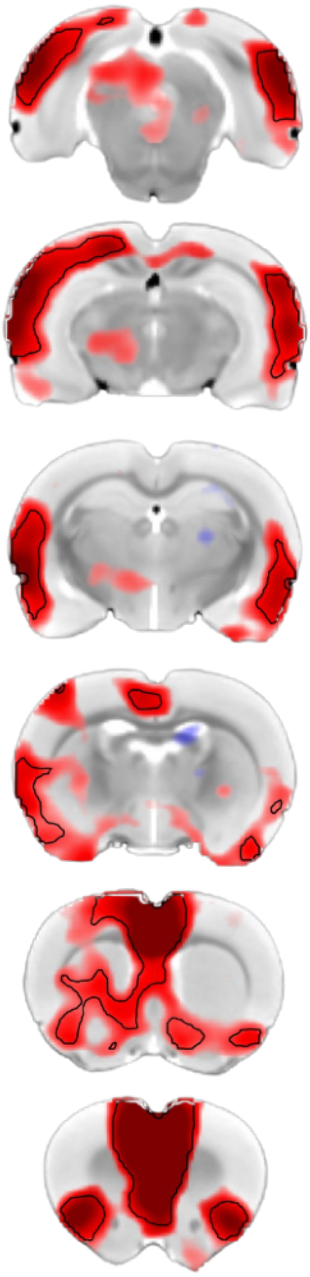
EEG: Capturing Electrical Signatures

EEG further enriches our insights by capturing the brain's electrical activity in real-time. This non-invasive technique records the electrical potentials generated by neural activity with exceptional temporal resolution. EEG is instrumental in helping us comprehend the brain's dynamics, from rapid responses to subtle modulations, and how they correlate with the changes induced by experimental drugs.

A Harmonious Ensemble of Insights

The true strength of our approach lies in the harmonious synergy among these techniques. BOLD fMRI gives us spatial context, ASL contributes hemodynamic details, and EEG offers exquisite temporal resolution. By combining their unique strengths, we achieve a comprehensive and integrated understanding of the intricate responses of the brain to experimental interventions. This fusion of methodologies enhances the translational value of your research, mirroring the techniques employed in clinical studies.

Seeing the Brain in Action: Functional Neuroimaging



Changes in connectivity in the prefrontal cortex due to effect of ketamine (seed correlation analysis of BOLD fMRI)

Introducing Functional Neuroimaging

Functional neuroimaging (fMRI), a core offering from L&M Data Science, transforms how we assess drug candidates during the pre-clinical phase. By using advanced imaging technologies, we enable pharmaceutical companies to visualise how experimental drugs interact with various regions, circuits, and networks in the brain. This newfound clarity accelerates our understanding of drug effects, helps predict potential outcomes and guides refinement of development strategies.

Understanding Functional Neuroimaging

Functional neuroimaging is a set of advanced non-invasive imaging techniques that capture real-time brain activity and connectivity patterns. Unlike traditional methods that provide static anatomical images, functional neuroimaging dives deeper, revealing the brain's actions and responses as they unfold. These techniques offer insights into the brain's functional landscape by observing changes in blood flow, metabolism, and neural connectivity.

Uncovering the Impact of Drugs

One of the most valuable applications of functional neuroimaging is its ability to shed light on how experimental drugs affect the brain. This is particularly crucial when developing treatments for neurological and psychiatric conditions, where drug-brain interactions determine therapeutic outcomes. Functional neuroimaging allows researchers to observe how drugs influence neural pathways, neurotransmitter systems, and overall brain function.

Mapping Neural Networks

Central to functional neuroimaging is its capacity to map neural networks. Functional magnetic resonance imaging and electroencephalography enable researchers to visualise brain regions that activate or deactivate in response to various stimuli, tasks, or drug interventions. These maps offer crucial insights into the brain's organisation and dynamics, aiding our understanding of disease manifestations and potential treatment interventions.

The Strength of Our Approach

Our **neuroPhINDr** platform offers a comprehensive solution to address pharmaceutical companies' challenges. Our high-throughput, standardised processes ensure efficient data collection and analysis. Our team of experts collaborates closely with clients to tailor our services to their specific needs. The result is a thorough characterisation of novel drug effects on the central nervous system, providing a solid foundation for decision-making throughout the drug development journey.

Data Acquisition: Using Multi-modality Measurements to Create a Comprehensive Picture of CNS Drug Effect

neuroPhINDr redefines comprehensive in-vivo drug characterisation within the central nervous system. This set of optimised and standardised procedures offers a meticulous approach to understanding how an experimental drug affects neural activity. **neuroPhINDr** provides a platform that balances precision with animal welfare, enhancing pre-clinical research methodologies by seamlessly integrating a series of steps performed on the same subject.

A Holistic Approach:

neuroPhINDr unfolds as a carefully choreographed sequence, each step designed to offer unique insights into drug effects while maintaining animal welfare:

1. **Light Sedation**: Light sedation ensures minimal animal stress, promoting stable conditions for accurate data acquisition. It is also crucial for preventing excessive movement during experiments.
2. **Structural Imaging**: High-resolution structural images lay the foundation for precise spatial analysis.
3. **EEG**: A pre-drug recording of the electrical activity creates a baseline picture of each subject's regular brain activity.
4. **Arterial Spin Labelling (ASL)**: By quantifying baseline blood flow, ASL adds hemodynamic insights into normal brain activity.
5. **Resting State MRI (rsMRI)**: Continuous BOLD fMRI acquisition (aka rsMRI) maps intrinsic brain connectivity and reveals standard networks before drug challenge.
6. **In-Scanner Drug Injection**: Drugs are administered remotely without disturbing the animal.
7. **EEG (post-drug)**: Continual monitoring captures dynamic changes in electrical activity post-drug administration.
8. **rsMRI (post-drug)**: Follow-up resting state scans provide a longitudinal perspective on brain network alterations.
9. **ASL (post-drug)**: A second ASL scan offers a comprehensive view of drug-induced hemodynamic changes.
10. **Blood/Tissue Sampling**: A concluding step to confirm drug concentration, validating the insights gained.

This comprehensive approach to drug effect characterisation helps us deeply understand the effects of experimental drugs on the brain while keeping the animals' welfare in mind.

Maintaining Stable Physiology: Enhancing Experimental Precision

When it comes to functional neuroimaging, it is crucial to maintain stable physiological conditions. Even slight changes in breathing, heart rate, or body temperature can introduce unwanted noise, obscuring the brain's responses to experimental stimuli. By prioritising stability, we can protect against misleading artefacts and ensure the reliability of our data.

Our Approach to Monitoring

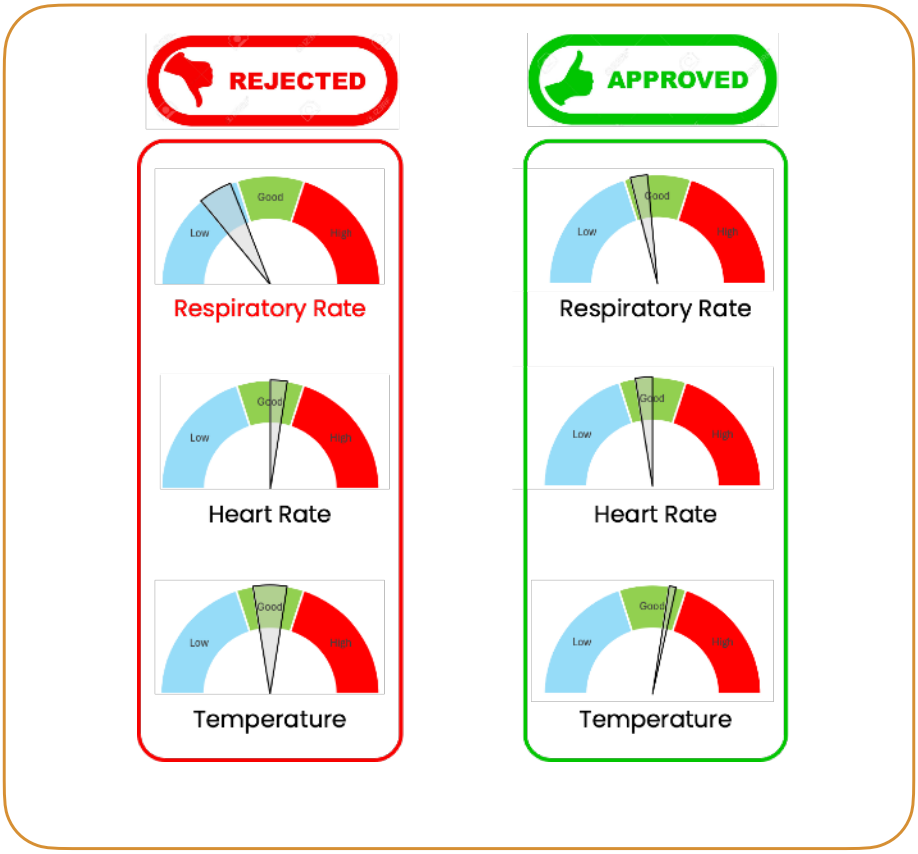
Our approach is centred on closely monitoring three key physiological indicators:

- **Respiratory Rate**: By carefully monitoring breathing patterns, we can ensure a continuous supply of oxygen to the brain, minimising disruptions to neural activity.
- **Heart Rate**: Monitoring heart rate ensures that experimental data is only acquired when appropriate blood flow is present. Consistent heart rate data enhances the accuracy of our findings.
- **Temperature**: Maintaining close observation and precise temperature regulation is imperative to prevent unintended fluctuations that may adversely affect brain activity and experimental outcomes.

By closely monitoring and managing these three parameters, we can ensure stability and depth of sedation are maintained throughout experiments, ensuring consistent physiological levels across experimental subjects.

To ensure the accuracy of each experiment, we strictly assess the physiological parameters obtained during data acquisition. Any subject that does not meet our rigorous acceptance criteria is automatically excluded from data analysis.

The first experiment was rejected due to lower than acceptable respiratory rate. The second experiment was accepted since all physiological parameters were whithin our acceptance range.



Data Processing and Quality Assessment: Making Sure Only the Highest Quality Data is Used

One of the central features of our **neuroPhINDr** platform is that it applies rigorous assessment of data quality for each subject, ensuring that the results we generate are reliable and accurate.

"By adhering to standardised acquisition protocols, we create the conditions for streamlined and automated analysis pipelines. This strategic approach accelerates processing times and enables us to deliver results swiftly. At L&M Data Science, efficiency meets precision, ensuring you receive actionable insights with remarkable speed."

Signal/Noise: We evaluate signal stability, levels, and background noise to gauge signal quality. By excluding data points that don't meet our rigorous standards, we ensure the reliability of our analyses.

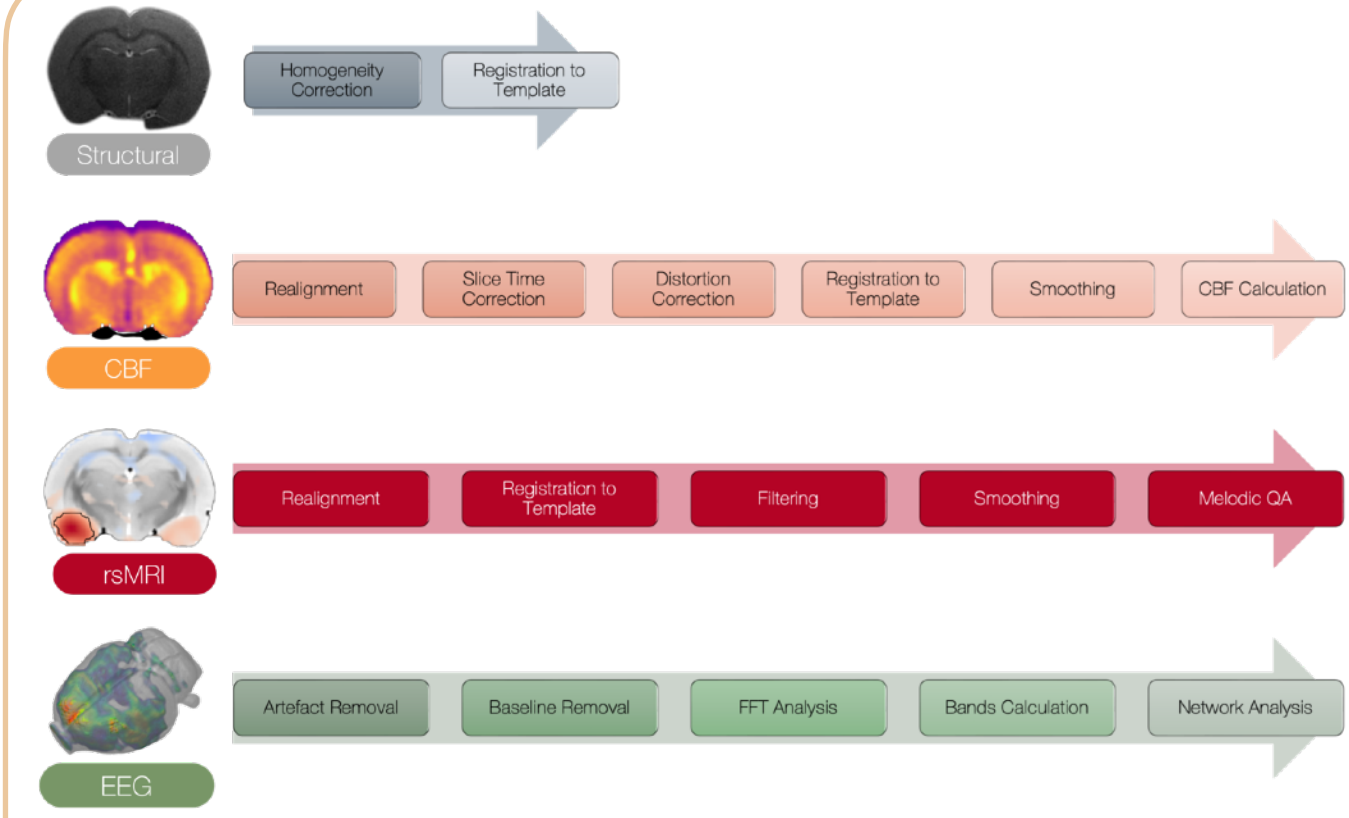
Movement: Even under appropriate sedation, slight movement may occur during data acquisition. Head movement is measured throughout the experiment to exclude data points with excessive displacement.

Spatial Registration: Spatial cohesion is paramount. Only images meeting our stringent registration criteria are utilised, preserving meaningful inter-subject comparisons.

Baseline Validation: Baseline cerebral blood flow (CBF) maps are compared with internal controls to confirm key regions are within expected parameters; Baseline EEG and fMRI connectivity also undergo comparison with our internal controls, ensuring robust brain function and connectivity before drug challenge.

Physiological Stability: Physiological parameters recorded throughout data acquisition are checked to ensure data integrity. Any outlier is promptly excluded, ensuring our datasets are of the highest quality.

Preprocessing Pipeline



Data Analysis: Investigating Every Angle, Building a Comprehensive Picture

- **Seed Analysis**: Involves choosing a key brain area ("seed") to study its connectivity patterns. By examining synchronised activity fluctuations, this method reveals neural networks and functional relationships between brain regions, shedding light on potential changes under experimental conditions.

- **Independent Component Analysis (ICA)**: It's a computational technique that disentangles the complex signals from different brain regions. It identifies unique patterns of activity, known as independent components, within the data. By isolating these components, ICA reveals distinct functional networks in the brain, providing valuable insights into its intrinsic connectivity and how it responds to various experimental manipulations.

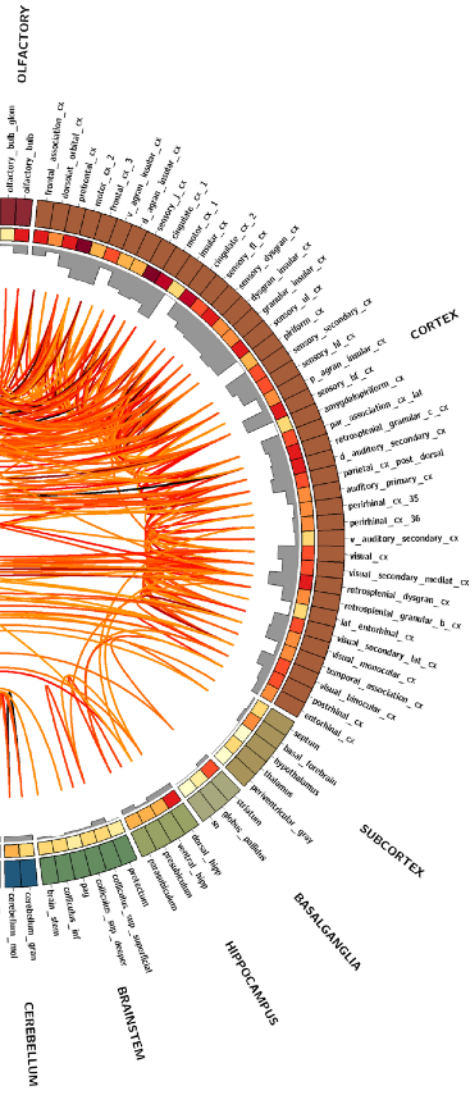
- **Network-Based Statistics** (NBS): This technique statistically quantifies the interconnections among distinct brain regions. In fMRI, it entails estimating the correlation between rsMRI signal fluctuations between pairs of brain regions; in EEG, it involves calculating these same correlations but using electrical activity from pairs of surface electrodes. These analyses reveal complex communication patterns between different parts of the brain. NBS helps us understand how the brain functions and works together, improving our understanding of how the brain processes information in various situations.

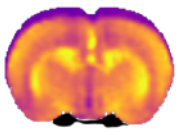
- **Graph Theory Analysis**: Involves modelling the brain as a network, where brain regions are nodes, and their connections are edges. It's like mapping a social network of interactions. By quantifying properties like node centrality and network efficiency, we can understand how information flows and how important specific brain regions are for overall brain function. This approach helps reveal the brain's intricate organisation and response to stimuli or conditions.

- **EEG Power Bands analysis**: Quantifies the distribution of brainwave frequencies, like sorting music notes into octaves. It reveals the strength of different frequencies—delta, theta, alpha, beta, gamma— providing insights into helping us understand cognitive states and neural activity patterns.

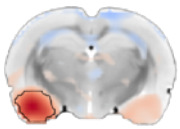
- **Cerebral Blood Flow (CBF) Maps**: Visualise the distribution of blood supply in the brain. They illustrate areas with varying levels of perfusion, providing insights into neural activity, potential abnormalities, and the effects of interventions.

- **Regions of Interest (ROIs)**: Using predefined, relevant brain regions, we extract the mean cerebral blood flow, enabling comparisons between groups in these specific areas.

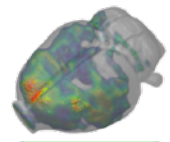




CBF



rsMRI



EEG

CBF maps
ROIs

Seed
ICA
NBS
Graph

Power Bands
NBS
Graph

L&M DATA SCIENCE

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We have full Access to state-of-the art facilities in four of the best pre-clinical MRI centres in Europe, where we implemented and validated our platform, **neuroPhINDr**.

Resources and Capabilities

Magnetic Resonance Imaging

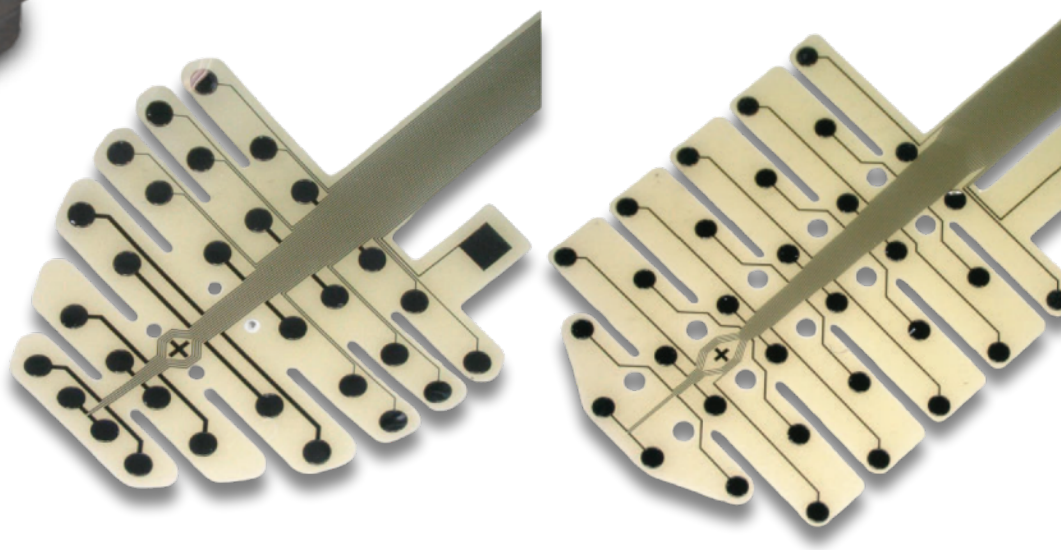
- 11.7T Bruker Biospin 117/16
- 9.4T Bruker Biospin 94/20
- 7T Bruker Biospin 70/30
- Assorted phased-array coils for rats and mice

Physiological Monitoring (SA Instruments)

- Heart Rate
- Respiratory Rate
- Temperature

Electroencephalography (EEG)

- OpenEphys Data Acquisition module
- Intan 32-channel Headstage
- Neuronexus 32-channel Surface Array



We also have access to a wide range of complementary techniques. Get in touch to learn more.

Navigating Innovation with L&M Data Science

Developing treatments for neurological and psychiatric conditions is a challenging task in the field of pharmaceutical innovation. Traditional methods are insufficient in comprehending the complexity of the central nervous system and its responses to experimental drugs. L&M Data Science is a pioneering partner that offers pre-clinical neuroimaging services to revolutionise drug development. Our innovative approach aims to provide a more effective solution to these challenges.

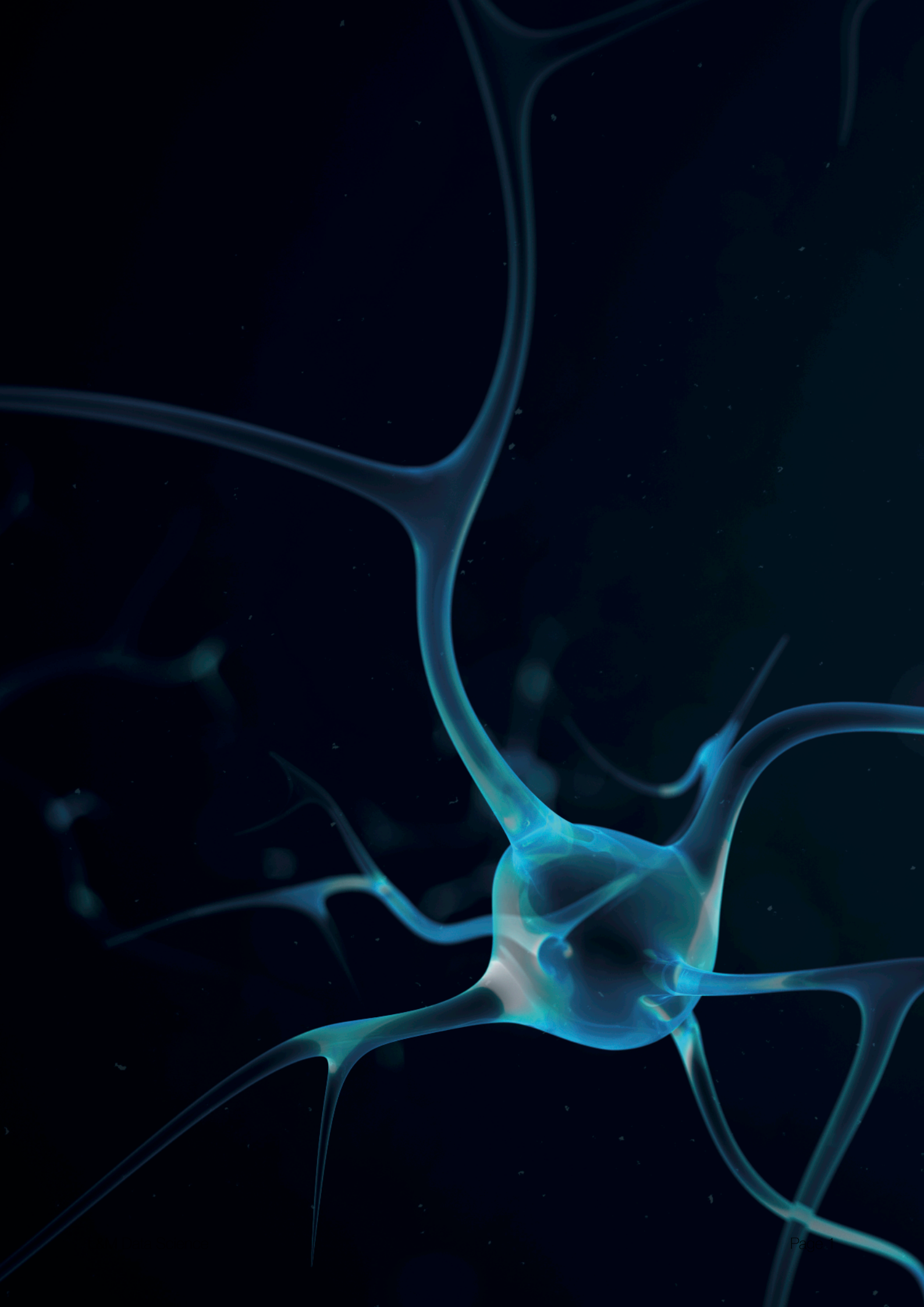
Our expertise in functional neuroimaging goes beyond anatomical images, allowing us to provide real-time insights into the activity and connectivity patterns of the brain. We understand the unique challenges of small animal studies and strive to balance the benefits of sedation with the authenticity of conscious observations. We promise to deliver value by reducing the time-to-results, increasing experiment reproducibility, and enhancing the translational value of your research.

Your Journey Awaits

At L&M Data Science, we believe that every discovery has the potential to change the world. Our commitment to precision, efficacy, and ethical research is unwavering, and we are eager to help you unlock the secrets of the brain and revolutionise drug development. With our efficient procedures and valuable insights, we are the perfect partner to join you on your journey of discovery. Let's work together to make a difference and create a better future for all.

The next step you take is crucial. Choose to explore the frontiers of pre-clinical neuroimaging with L&M Data Science. Contact us today and embark on a journey of innovation, precision, and purpose. Together, let's redefine the landscape of neurological and psychiatric treatments, shaping a future where breakthroughs become realities and lives are transformed. Your journey to discovery starts now.

Michel Mesquita
CEO



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