

Mass Spectrometry Imaging Drives Research into Parkinson's Disease

Parkinson's disease is a progressive neurological disorder that affects movement in the body. With a study published in *Nature Medicine* indicating that more than 57 million people across the globe suffer from neurodegenerative disease, a figure expected to double every 20 years as the population ages, it is imperative to further our understanding of the causes of Parkinson's disease, as well as the conflicting side effects of a therapeutic drug used to alleviate its symptoms.¹

The capability of mass spectrometry imaging (MSI) to detect a range of neuroactive compounds and metabolites in a single tissue section has firmly established its potential in neuroscientific research. This article will explore the ground-breaking research by the Spatial Mass Spectrometry group at Uppsala University in Sweden, one of the largest centres for life sciences in Europe, into Parkinson's disease, specifically a specific stage of the disease, called levodopa (L-DOPA)-induced dyskinesia (LID), which develops in approximately 50 percent of patients after five to six years of L-DOPA treatment.

A Deeper Understanding of Parkinson's Disease

Parkinson's disease is an incurable neurodegenerative disease caused by the loss of dopamine-producing nerve cells in the brain. It is characterised by motor dysfunction, tremors, bradykinesia (or slowed movement), muscle rigidity, and postural instability including involuntary and unpredictable body movements.

L-3,4-dihydroxyphenylalanine (levodopa, or L-DOPA) administration is the primary treatment for Parkinson's. L-DOPA is a precursor to dopamine that crosses the blood-brain barrier where it is converted into dopamine, replenishing the brain's depleted supply of dopaminergic neurons in the substantia nigra pars compacta region that leads to reduced dopamine in the striatum, an area of the brain responsible for movement control in the body.

L-DOPA is highly effective in the early stages, but its long-term use is often accompanied

by the side-effect LID, a treatment-limiting complication which exhibits as involuntary, erratic, and uncontrollable tremors and whose pathophysiology is poorly understood.

LID has a significant negative impact on quality of life. What is not yet known is why only certain people are affected. Working with animal models, as well as human blood-cerebrospinal fluid (CSF) biobank samples supplied by collaborators at the Karolinska Institute, Stockholm, Bordeaux University, and Kings College London, researchers in the Department of Pharmaceutical Biosciences at Uppsala University are using MSI to investigate the elevated L-DOPA levels in the brain that are linked with LID.

The MSI Advantage

MSI is an advanced, label-free mass spectrometry tool that can be used to map the spatial distribution of molecules such as lipids, proteins and metabolites directly within thin tissue sections.

MSI can be integrated with microscopy or histology, and provides an additional parameter for identification over traditional MS by enabling the accurate simultaneous determination of multiple tissue distributions. This allows quantitative regional mapping, and high resolution visualisation of molecular change to support neurodegenerative disease research.

The research at Uppsala is focused on imaging the spatial distribution of neurotransmitters, or the signalling molecules in the brain, that are known to be affected in Parkinson's disease. The group has developed a method to image neurotransmitters in a specific brain region, at the same time providing a new view of the brain and the transmitters involved in current Parkinson's disease models. This method, using MALDI MSI, has enabled researchers to measure and quantify different neurotransmitters, and their metabolites and precursors, simultaneously.

MSI Supports Identification of Elevated Brain L-DOPA Levels

A study used ultrahigh mass resolution Fourier transform ion cyclotron resonance (FTICR) matrix-assisted laser desorption/ionisation (MALDI) MSI (7T solarix XR)

to map the distribution of L-DOPA and monoaminergic pathways in the brains of dyskinetic and nondyskinetic animal models.² Fourteen neurotransmitters and metabolites were simultaneously imaged and identified with accurate mass.

Elevated levels of L-DOPA and its metabolite 3-O-methyldopa were found in all measured brain regions of dyskinetic animals, and increases in dopamine and metabolites were noted in all regions analysed, except the striatum.

It was found that LID is linked to a dysregulation of L-DOPA metabolism throughout the brain: the inability of extrastriatal brain regions to regulate the formation of dopamine during L-DOPA treatment introduces the potential of dopamine, or L-DOPA itself, to modulate neuronal signalling widely across the brain, causing unwanted side effects.

Neuropeptides Demonstrate Link With LID

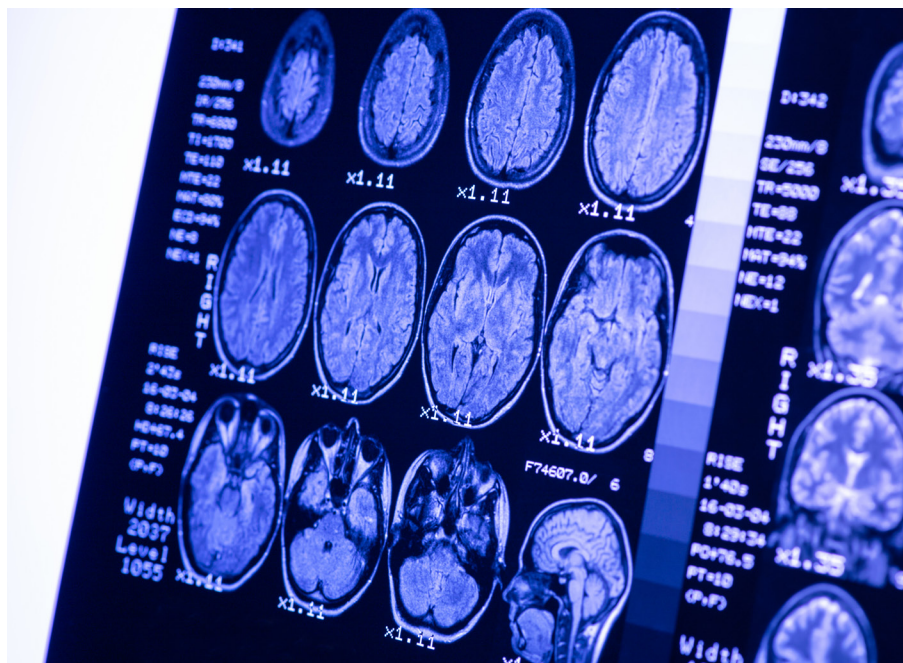
Parkinson's disease and LID have both been linked with altered expression of neuropeptide precursor messenger ribonucleic acids (mRNA).

An investigation into the basal ganglia neuropeptides that have been associated with LID development found that dyskinesia severity correlated with elevated levels of some abnormally processed peptides in multiple brain regions.³

Dynorphin, enkephalin and tachykinin neuropeptides of the basal ganglia have many effects, including regulation of neurotransmitter release, modulation of blood-brain barrier permeability and stimulation of neuro-inflammatory responses.

MALDI-MSI was used to characterise neuropeptide alterations in the same pre-existing cohort of samples from an animal model of Parkinson's disease during the peak LID behaviour period, targeting the depletion of catecholaminergic neurons to closely mimic symptoms of Parkinson's and LID.

In the study, MALDI-MSI was used to image and identify 23 neuropeptides, as



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well as image and analyse the effect of LID on these neuropeptides in the brain. It was found that LID was associated with an increase in the multiple neuropeptide levels across the basal ganglia structures, while non-LID animals had low levels of these neuropeptides. The severity of LID correlated with the abundance of processed derivatives of the active neuropeptides in certain basal ganglia regions, and putaminal levels of L-DOPA correlated with the abundance of the active neuropeptides, but did not correlate with the levels of processed derivatives, suggesting that striatal L-DOPA itself may induce neuropeptide signalling, without first being converted to dopamine.

Lipid Dysregulation

As lipids are increasingly considered a prominent class of metabolites in neurodegenerative disease research, lipidomics has become an important metabolomics research pathway. Lipids are strongly linked to many aspects of Parkinson's disease, but there are few studies on their impact on LID-specific changes.

High resolution MSI was used in a study to map brain region-specific alterations of glycerophospholipids and sphingolipids in the same animal model of Parkinson's with and without LID following long term L-DOPA treatment.⁴ Spatial lipidomic analysis identified region-specific lipid dysregulation as a novel aspect of LID pathology, highlighting lipid pathways as potential targets for future research.

LID was associated with depletion of antioxidant ether phosphatidylcholines and

altered PUFA-containing glycerophospholipids in regions critical for motor function, which differed from similarly treated non-dyskinetic animals, suggesting lipid composition mediates differential susceptibility to LID. Lipid alterations correlated strongly with dyskinesia severity, dopamine and L-DOPA concentrations, supporting a mechanistic link between lipid metabolism, neurotransmitter dysregulation and LID.

Building a Better Understanding of LID

The new workflows for imaging neurotransmitters will continue to support neuroscience research using MSI.

Adopting an integrated spatial omics approach that combines MSI with spatial transcriptomics and spatial proteomics facilitates precise measurements of metabolites across brain tissue regions. These advances will continue to support fundamental research into the mechanisms underlying Parkinson's disease and treatment response.

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Dr. Per Andrén

Mass spectrometry veteran Dr. Per Andrén was a postdoc in the group of Professor Richard Caprioli, in the early days of electrospray ionisation, and became the world's first Professor of Mass Spectrometry Imaging, at the Department of Pharmaceutical Biosciences, Uppsala University, Sweden, having originally gained his MSc in Pharmacy and PhD in Medical Sciences (Psychiatry) at Uppsala University. Today, Dr. Andrén is interested in the use of MSI for the analysis of biological systems and focuses on MSI method development in applications for the brain and neurodegenerative diseases, with a particular emphasis on Parkinson's disease.



Dr. Michael Easterling

Dr. Michael Easterling is Vice President of MALDI Imaging at Bruker Daltonics. Following his PhD in Chemistry from The University of Georgia, Dr. Easterling has worked at Bruker Daltonics for almost 25 years, specialising in MALDI mass spectrometry. Dr. Easterling focuses on multimodal spatial analysis, more recently integrating mass spectrometry imaging with transcriptomics and proteomics to advance understanding of complex biological systems, including neurodegenerative disease.

Rethinking CNS Drug Development: From Symptom Control to Durable Brain Health

Central nervous system disorders present one of the greatest challenges in life sciences today.

They are the Everest of medicine – stubborn, unyielding, awkward; still unconquered many decades after other seemingly impenetrable horizons have been comprehensively mapped, even if they haven't been entirely tamed.

Like that giant looming above us, CNS disorders present a series of particular challenges that require huge amounts of highly technical know-how, teamwork, the sharing of ideas, a great deal of trial and error – and persistence.

In fact, so unique is each disorder that each is like its own vast mountain, its own world of problems to be learned and hopefully mastered – and the CNS field more like the whole Himalayan range stretching on and on.

Nonetheless, they share common problems for drug developers: their biology is often complex; diagnosing them can be difficult – especially early in the course of disease; so too can be measuring their severity and how they are progressing.

While oncology, immunology and rare disease medicine have been reshaped by molecular stratification, biomarkers and targeted therapies, progress in most CNS indications has been slower and less predictable.

In disorders of the brain, the target is rarely a single impaired component. More often, disease emerges from disrupted networks: genetic vulnerability, altered synaptic signalling, neuroinflammation, neuroplasticity imbalance, vascular dysfunction, environmental effects and ageing biology may all contribute to different combinations. That makes CNS drug development less like replacing a faulty part and more like trying to retune a highly adaptive system.

The Problem of Translation

As mentioned above, the first major challenge is biological complexity. Many CNS diseases

are not driven by one pathway in the way that some monogenic or oncology indications can be. Even where a clear genetic driver exists, as in fragile X syndrome – the most common inherited cause of intellectual disability – the downstream effects can extend across synaptic function, RNA translation, mitochondrial biology, dendritic spine development and broader neural network pattern. Recent proteomics work in fragile X syndrome, for example, has discovered that individuals exhibit a wide range of dysregulated proteins which are thought to negatively affect synaptic plasticity and cellular function. This reinforces that CNS diseases need to be understood at the systems level rather than through a single target alone.

This creates a second challenge: modelling. Quite simply, modelling how the brain works, what happens when compromised by a disease, and how a drug might affect it, is extremely difficult. Traditional cell systems can be useful for testing defined molecular hypotheses, but they cannot reproduce the three-dimensional organisation, cellular diversity and dynamic signalling of the human brain. Animal models remain essential, particularly for understanding circuitry and behaviour, but species differences in brain development, cognition and disease progression limit their translatability value. As a result, encouraging preclinical findings often fail to translate into meaningful clinical benefit.

We are getting better at this. Sophisticated new tools such as human induced pluripotent stem cell models, brain organoids, assembloids, organ-on-chip systems and multi-omics profiling are helping us bridge this gap. Yet these platforms are not fully mature, nor are they ever likely to be replacements for clinical evidence, however good they get. They might, however, help developers identify more human-relevant mechanisms, test therapeutic hypotheses earlier and better understand why particular subgroups of patients respond differently.

Biomarker Breakthroughs? Measuring What Matters

A third and closely related obstacle is measurement. In many CNS disorders,

diagnosis still depends heavily on clinical observation, symptom scales and patient or caregiver reporting. These tools are important, but they are often subjective, variable and fail to spot early biological change.

For progressive neurodegenerative diseases such as Alzheimer's and Parkinson's disease, to name just two, the underlying pathology often begins years before symptoms emerge. Once symptoms are obvious, the underlying neurodegeneration has usually progressed substantially.

Neurodevelopmental and psychiatric disorders are different, and while they might not be characterised by a 'silent sleeper' problem they come with their own diagnostic and measurement challenges. Meaningful clinical change may involve altered cognition, social interaction, behaviour, daily functioning, sleep, anxiety, learning or caregiver burden. Such variables are not always captured cleanly by conventional endpoints and can be extremely subjective too.

This is one reason why biomarkers are becoming central to development of CNS therapeutics. In Alzheimer's disease, the field has moved furthest, with imaging and cerebrospinal fluid markers now complemented by increasingly accurate blood-based biomarkers such as plasma phosphorylated tau.

The broader lesson extends beyond Alzheimer's. Reliable biomarkers will help us identify patients earlier, stratify heterogeneous populations into more homogenous sub-groups, confirm target engagement, monitor disease progression and provide supportive evidence of therapeutic response. Without them, trials risk enrolling biologically mixed populations – diluting treatment effects, extending timelines and leading to costly and dispiriting failures.

Digital biomarkers could also become increasingly important too. Wearables, smartphones and remote monitoring tools can collect high-frequency data on movement, sleep, activity, cognition and behaviour in real-world settings – helping monitor chronic neurological conditions in real time, where clinic visits provide only



snapshots. However, digital measures must be standardised, clinically meaningful and accepted by regulators before they can really change drug development.

The Blood-Brain Barrier

Even when the biology is understood and the right patient population can be identified, CNS drug delivery remains a major hurdle. That's due to the blood-brain barrier, which protects the brain from toxins and pathogens, but it also limits the entry of many therapeutic agents, particularly biologics and larger molecules.

It's tempting to call this hurdle the Hillary Step of CNS disorders, but that would be misleading. Overcoming the blood-brain barrier is more like just getting to base camp with all the kit you need for the ascent intact.

The blood-brain barrier has shaped the CNS pipeline for decades, and chances are, it will do so for decades to come. Small molecules with favourable brain penetration remain attractive, but not every biological target is readily druggable by a conventional small molecule.

The barrier means that other modalities such as gene therapies, antisense oligonucleotides, antibodies and RNA-based approaches usually require invasive administration or specialised delivery

technologies. New approaches – including receptor-mediated transport, nanoparticles, intrathecal delivery, intranasal delivery and focused ultrasound – are being explored, but each brings its own safety, scalability and regulatory considerations. They are in the foothills of development.

The delivery question is therefore not merely technical. It influences target selection, modality choice, dosing, patient burden and commercial feasibility. A therapy that is biologically elegant but difficult to administer repeatedly may face challenges in chronic diseases requiring long-term treatment.

From Symptoms to Systems

Despite this challenging backdrop, progress is being made. We are higher up the mountain than we were. The aim of many drugs in development today is not merely symptom suppression – important as that is – but restoration of underlying brain function. This is particularly evident in the growing interest around neuroplasticity.

Neuroplasticity is the brain's capacity to change its structure, function and connectivity in response to internal and external stimuli. It underpins learning, memory, adaptation and recovery. In disease, however, plasticity can be impaired, excessive or misdirected. In neurodevelopmental disorders, abnormal synaptic development and altered network

maturation may affect cognition and behaviour. In neurodegeneration, loss of synaptic resilience may contribute to functional decline. In mental health disorders, maladaptive circuit activity may reinforce persistent symptoms.

The therapeutic opportunity is not simply to “boost” plasticity. The brain's adaptability is powerful precisely because it is regulated. Impaired plasticity may limit learning and recovery; too much or poorly directed plasticity modulation may destabilise circuits – causing undesired adverse events. A more promising concept is restoration of plasticity balance, thus supporting healthier synaptic and network function in a way that translates into durable benefit.

In fragile X syndrome, this systems-level thinking is particularly relevant. The condition arises from loss or deficiency of FMRP, an essential RNA-binding protein that regulates protein synthesis in the brain. FMRP deficiency might be the trigger, but the clinical effects reflect broad downstream disruption in synaptic signalling, dendritic spine maturation and network function. This helps explain why highly selective approaches aimed at individual pathways have so far struggled to deliver consistent disease-modifying benefit. It also supports growing interest in approaches that address circuit-level dysfunction and adaptive brain function more broadly.



Precision Medicine

Precision medicine is revolutionising other medical fields, such as oncology, where the type of genetic mutation a tumour carries might now dictate the treatment strategy.

In CNS medicine genetics won't always be the way we subdivide patients into groups, but the same principle is being applied: better matching so the right patients get the right treatment at the right time.

This approach will require integration of multiple data types. Genetics might identify causal mechanisms in rare neurodevelopmental disorders. Imaging might reveal network or structural changes. Fluid biomarkers might indicate underlying pathology. Digital measures might capture real-world function. Clinical and behavioural data might define meaningful outcomes for patients and families. Artificial intelligence and machine learning could help interpret these multimodal datasets, although their use must be transparent, validated and clinically interpretable.

Early Diagnosis and Intervention

In many neurodegenerative diseases, by the time symptoms are clear, substantial damage has already occurred. Meanwhile, in neurodevelopmental conditions, intervening earlier is likely to influence developmental trajectories more. Diagnosing disease early is therefore of paramount importance –

although not straightforward. The technical, economic and ethical challenges are considerable. Is a test accurate? Is it cheap enough to be rolled out at scale? Even if it meets these criteria, can anything be done for those we identify with the disease?

Regulation and Collaboration

Nonetheless, the direction of travel is clear. We are beginning to make strides towards identifying CNS disorders earlier, more precisely, and beginning to develop therapies for them that have disease-modifying potential. All this is good.

To go further – to climb higher – the regulatory environment will be critical. Developers need clarity on how biomarkers, digital tools, adaptive trial designs and novel preclinical models can support decision-making. Regulators, in turn, need robust evidence that these tools are reliable, reproducible and linked to outcomes that matter.

Adaptive and platform trials may help in heterogeneous diseases by testing multiple interventions or patient subgroups more efficiently. Decentralised trials could help boost recruitment, speed up trials and reduce the burden on patients and caregivers. Collaborations will also play an important role by enabling greater data sharing and reducing duplication of effort. This will be particularly important in rare or high-risk

indications where no single organisation can solve the problem alone.

Towards Durable Outcomes

Ultimately, progress in CNS medicine should be judged not only by whether symptoms improve over weeks or months, but by whether treatments change the trajectory of disease and daily life. In neurodegeneration, which could mean slowing decline, preserving independence or delaying the need for care. In neurodevelopmental disorders, it might mean sustained gains in learning, communication, behaviour, social participation and family functioning. In mental health, it may mean longer-lasting recovery, reduced relapse and improved ability to work, study and maintain relationships.

This is where neuroplasticity, biomarkers and precision medicine converge. The goal is not simply to produce more CNS drugs, but to produce treatments developed with stronger models, tested in better-defined patients, measured with more meaningful tools and aimed at outcomes that last.

The brain is not a static organ. It changes throughout life, for better and worse. The next phase of CNS drug development will depend on learning how to measure, guide and restore that change with far greater precision.

The next phase might not take us to the peak, but it will raise us higher up, and from there we will have a clearer view of the challenges ahead.



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Translating Clinical Evidence to Advance N2B Drug Development

For decades, nose-to-brain (N2B) drug delivery has offered an attractive proposition as a non-invasive means of reaching the central nervous system (CNS) while reducing reliance on transport across the blood-brain barrier.^{1,2} The scientific rationale has been supported by extensive preclinical research yet one fundamental question has continued to limit clinical confidence: can a molecule administered through the nose be shown to reach relevant regions of the human brain?^{2,3}



Nasal administration is already established in several CNS-related conditions, including epilepsy, migraine, depression and opioid overdose.⁴ These products demonstrate many of the advantages that continue to drive interest in the nasal route, offering a non-invasive, easy-to-use alternative to injectable administration while providing a similarly rapid onset of action.^{4,5} Most, however, primarily depend on absorption through the nasal mucosa into the systemic circulation, with CNS exposure achieved after the active molecule crosses the blood-brain barrier.⁵⁻⁷

Direct N2B delivery has a different objective. It seeks to use the anatomical connections of the olfactory and trigeminal pathways to transport therapeutics from the nasal cavity to the CNS.⁸ Interest in this approach is increasing as the development pipelines expand to include peptides, proteins and other molecules with limited blood-brain barrier permeability.^{1,5} It is also being driven by demand for patient-friendly treatments capable of achieving rapid and meaningful CNS targeting while reducing systemic exposure and the associated risk of peripheral effects.^{1,2}

Recent human imaging studies have now provided direct evidence of N2B transport in humans. As a result, the development question is no longer limited to whether this pathway exists.⁹ Attention is increasingly turning to how reliably it can be achieved, which factors influence delivery in different individuals and how the formulation and delivery system can be configured to improve performance.

The Challenge of Human Validation

Before this direct human imaging data became available, N2B delivery had long generated scientific interest but translation into clinical development was constrained by two related challenges: 1) demonstrating that a molecule reached the human brain and 2) achieving sufficiently consistent administration to interpret therapeutic outcomes.^{2,10}

Preclinical studies have provided substantial evidence that compounds can move from the nasal cavity into the CNS along pathways associated with the olfactory and trigeminal nerves.² However, evidence of transport in an animal model does not necessarily establish how a formulation and delivery system will perform in humans.¹⁰ Differences in nasal anatomy, administration technique, formulation behaviour and disease-related physiology may all affect the amount, location and timing of brain exposure.^{2,10,11}

This uncertainty has made it difficult to separate the performance of a therapeutic molecule from the performance of its delivery method. If a clinical study does not produce the expected therapeutic response, it may be unclear whether the underlying biological hypothesis was incorrect or whether the administered dose failed to reach the intended CNS regions consistently.² Early clinical experience illustrates this challenge: in the SNIFF trial with intranasal insulin, a change in delivery system during the study was associated with different clinical outcomes, highlighting how administration can complicate interpretation of therapeutic efficacy.¹²

This field is consequently moving towards system-level approaches supported by direct human evidence. Rather than treating the nasal spray system as a passive container, developers are increasingly considering formulation properties, spray performance, deposition location and user interaction as interdependent elements of the therapeutic strategy. By leveraging human imaging, researchers can evaluate the *in vivo* performance of the device-formulation platform, providing a deeper understanding of the nasal delivery system and creating new opportunities for optimisation.

A Step Towards Evidence-Driven N2B Development

A first-in-human PET study by researchers at Wake Forest University demonstrates how human imaging can be applied to evaluate N2B delivery *in vivo*.⁹ The investigation evaluated the safety, kinetics and regional distribution of intranasally administered radiolabelled insulin in 16 older adults (mean age 72 years) who were either cognitively normal or had mild cognitive impairment (MCI). Researchers administered the novel PET radiotracer using Aptar Pharma's Cartridge Pump System (CPS), followed by a 40-minute dynamic PET scan to quantify regional brain uptake over time. A positioning guide was used to align the system with the nasal septum and increase the likelihood of deposition towards the superior turbinate and olfactory-regions.

The importance of the study lies beyond insulin itself. PET enabled researchers to visualise and quantify brain uptake over time rather than inferring delivery solely from

clinical outcomes or peripheral measurements. It therefore provided information about the performance of an established nasal delivery system in a human N2B application and created a basis for further investigation and optimisation.

What the Study Reveals About Human N2B Delivery

Brain delivery is achievable. Following administration, radiolabelled insulin was detected in multiple regions associated with cognition and Alzheimer's disease pathology, including the hippocampus, amygdala and temporal cortex. These findings provide direct human evidence that biologically active molecules can be delivered from the nasal cavity to anatomically distinct regions of the brain, supporting the translational relevance of the olfactory and trigeminal pathways previously identified in preclinical studies.⁹

Delivery is rapid and measurable. PET imaging showed that radiolabelled insulin reached the brain shortly after administration, with most uptake and clearance occurring within the 40-min imaging period.⁹ This temporal PET signal reflects the kinetics of brain delivery and radiotracer clearance rather than the duration of insulin's biological activity, which may continue through receptor binding and downstream signalling.^{13,14} These findings provide direct insight into CNS delivery kinetics following intranasal administration, representing an important step towards defining CNS pharmacokinetics and informing rational dosing strategies.

Delivery varies across individuals. Significant brain uptake was observed across the cohort, but the timing and extent of uptake were associated with physiological and clinical characteristics. Importantly, uptake in the MCI group generally peaked earlier, declined more rapidly and was lower across the evaluated brain regions. These findings suggest that N2B delivery is influenced not only by the administered therapeutic and delivery system, but also by individual biology and the integrity of the underlying transport pathways.⁹

Delivery can limit systemic insulin exposure. No major safety concerns were identified. Plasma insulin levels did not change significantly following administration, blood pressure remained stable and glucose levels remained above the threshold for hypoglycemia.⁹ Although the study was not designed to evaluate long-term safety or repeated administration, the findings provide



initial human evidence that CNS delivery can be achieved without substantial systemic exposure.

Taken together, the results demonstrate both the feasibility of human N2B delivery and the complexity of achieving consistent exposure across populations. By providing direct evidence of CNS transport in humans, imaging studies such as this one may also help distinguish whether an apparent lack of observable effect reflects the underlying therapeutic hypothesis, insufficient or inconsistent delivery to the intended CNS regions or a combination of both. This distinction could support more informed development decisions by reducing uncertainty around whether the drug or the delivery approach is limiting clinical performance. The study also provides an early indication of how delivery-related variability may be addressed: its use of a positioning guide to target the upper-nasal cavity illustrates the importance of administration strategy alongside formulation as the field moves beyond proof of concept towards optimising performance. Future progress will therefore depend not only on improving the consistency and targeting of delivery, but also on understanding how molecular characteristics influence transport and CNS exposure.

The Challenge of Consistent and Targeted Delivery

The nasal cavity presents a demanding environment for targeted drug delivery. Its internal geometry is complex, and the olfactory-region occupies only a small area high within the nasal cavity.⁵ Successful deposition depends on both device performance and user technique, including factors such as spray angle, insertion depth

and spray characteristics, particularly when precise targeting of the upper-nasal cavity is required.^{2,5}

Conventional nasal spray pumps, including the CPS used in the PET study, were primarily developed for local or systemic applications, where broad deposition within the nasal cavity is often sufficient. N2B delivery presents a different engineering objective because effective engagement of the relevant neural pathways depends on reaching the olfactory and upper turbinate regions more reliably.^{2,11}

The PET findings demonstrate that the CPS could support measurable N2B delivery, but they also highlight why delivery performance must be interpreted in context. The use of a positioning guide to improve targeting of the upper-nasal cavity reflects efforts to standardise administration and minimise user-related variability during delivery.⁹ There is therefore growing interest in configurations that can build on these established nasal technologies while further improving upper-nasal deposition and reducing dependence on highly precise user technique.

Treating N2B Delivery as an Integrated System

Traditional pharmaceutical development often begins with the therapeutic molecule, with the delivery device selected later in the process. For N2B programmes, however, this sequence may create avoidable risk. Formulation properties, spray performance and user handling can all influence the effectiveness and reproducibility of drug delivery. This creates a need for delivery solutions designed to address the unique physiological and technical demands of N2B administration, while supporting more

precise, reproducible and clinically relevant CNS delivery.¹⁵

As N2B drug development matures, administration strategy is becoming increasingly important to improve confidence in development decisions, strengthen clinical interpretation and reduce programme risk. As a result, N2B delivery should be treated as an integrated system involving the formulation, pump, actuator and administration procedure. Consideration of human factors is particularly important because relatively small changes in insertion depth or orientation may alter the location of deposition. Accordingly, device–formulation co-development, informed by administration strategy and human factors, is increasingly being recognised as critical to optimising therapeutic performance and advancing development-ready N2B strategies.

Evolving N2B Platforms: Validated Foundations and Purpose-Configured Targeting

To support this integrated development approach, Aptar Pharma has introduced NeuroSpray™, a purpose-configured multi-dose platform specifically engineered for CNS applications. Building on clinically established platforms, including the CPS used in the landmark first-in-human PET study, NeuroSpray™ combines validated delivery technology with design features intended to support more consistent upper-nasal targeting without the need for external positioning accessories.

Compared with conventional nasal spray configurations, NeuroSpray™ incorporates a narrower, more concentrated spray plume to better align with the targeting requirements



of upper-nasal delivery. Pre-compression actuation supports more controlled and reproducible spray generation while reducing run-off, thereby increasing contact time within the intended deposition region.

NeuroSpray™ was also developed with human factors considerations integrated directly into the system design. Ergonomic controls and nostril-positioning features were incorporated to reduce sources of real-world variability, such as nasal alignment, insertion depth, orientation errors and the risk of misuse. Together, these elements aim to reduce reliance on perfect technique while supporting patient comfort and usability across diverse patient populations.

The platform has been evaluated through a combination of preclinical, performance and human factors studies to characterise its delivery performance under clinically relevant conditions. These internal studies

have demonstrated targeted upper-nasal deposition, reproducible administration and usability under real-life conditions. For example, in vitro testing using a low-viscosity placebo formulation has shown olfactory-region deposition of up to 50% under varied spray angles with NeuroSpray™, compared with approximately 1–5% for the standard pump configuration.²

Collectively, these capabilities demonstrate how an integrated device–formulation approach can support more consistent CNS-focused administration across diverse formulations and clinical programmes, helping to advance the development of non-invasive CNS therapies.

Implications for Future Drug Development

Purpose-configured delivery platforms such as NeuroSpray™ represent one example of how advances in administration technology can complement emerging human evidence. More broadly, they illustrate the direction in which N2B development is evolving, from demonstrating biological feasibility toward systematically optimising delivery performance.

To address this growing need to validate delivery performance alongside therapeutic efficacy, NeuroSpray™ helps developers incorporate delivery configuration into the N2B development strategy. Device–formulation co-development, supported by deposition modelling, in vitro testing, imaging and human factors evaluation, can help characterise CNS exposure and guide development to help reduce uncertainty earlier in development.

Conclusion

N2B delivery is becoming a more structured and evidence-driven development field.

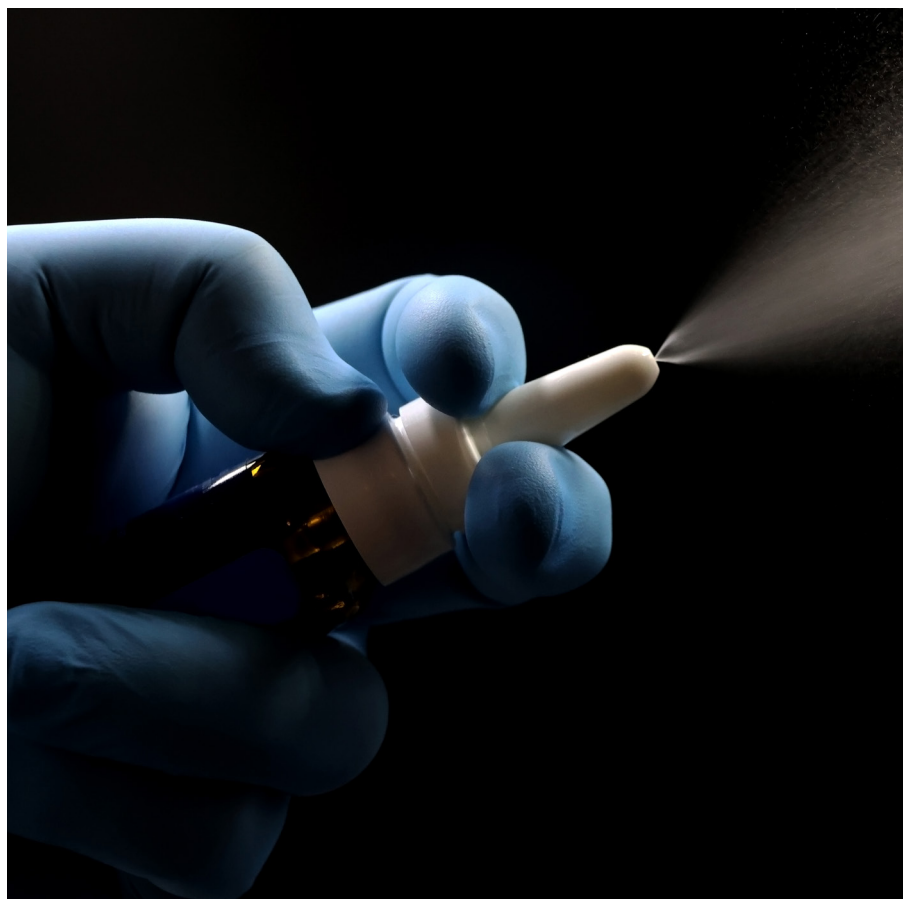


Human PET imaging has now demonstrated that intranasally administered insulin can reach multiple cognition-related regions of the brain, while also revealing differences in uptake associated with cognitive status and other biological variables. These findings validate the feasibility of the route but reinforce the need for larger studies, deeper investigation of patient variability and stronger control of upper-nasal deposition.

Progress will depend on integrating molecular science with formulation development, device engineering, imaging and human factors. As N2B drug development evolves, device-formulation co-development offers a framework for integrating these elements into a single therapeutic strategy. Platforms such as NeuroSpray™, which combine purpose-engineered delivery technology with human factors and performance validation, illustrate how this approach may help improve delivery consistency while supporting the development of non-invasive, patient-friendly CNS therapies.

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