



WHITE PAPER

# Beyond the Canonical Motor Syndrome

**Non-motor and non-canonical features of Parkinson's disease**

A Framework for Translational Modeling in Parkinson's Disease: Symptom architecture, circuit-state instability, and the design of translational preclinical models

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## **Parkinson's disease (PD) remains largely recognized and clinically diagnosed by its motor symptoms. However, many of the problems that dominate daily life for patients fall outside that definition.**

Sleep fragmentation, cognitive slowing, anxiety, pain, loss of motivation, autonomic dysfunction, and gastrointestinal symptoms can appear long before formal diagnosis, fluctuate independently of motor state, and become major determinants of independence and caregiver burden. These non-canonical features create opportunities to evaluate therapies now while also exposing where many current models and endpoints remain weak. This white paper sets out how Atuka approaches the route from a patient problem to a defensible choice of model, endpoint, and interpretation.

Five main ideas run through the paper. First, that functional burden is shaped by symptoms acting together. Motor impairment, sleep, cognition, motivation, pain, autonomic function, treatment state, and the work of compensation interact. A person may preserve outward performance while drawing increasingly heavily on the resources needed to sustain it. Figure 1 illustrates why total disability cannot be solely understood from a motor score or a list of isolated symptoms.

Second, the pattern of symptoms may also tell us something about the disease. The order and combination of sleep, autonomic, affective, and cognitive changes do not yet define reliable biological subtypes. They may nevertheless provide clues to disease route and trajectory and give us a reason to study symptom architecture rather than treating every feature as an independent outcome.

Third, circuit function is dynamic. The same anatomical system can occupy different states as pathology, treatment, context, and demand change. Dysfunction may appear over seconds, as during a freezing episode, or emerge over years as compensation and

reserve decline. For many non-canonical features, the important experimental question is therefore not only whether a deficit is present, but when the system moves from compensation to failure, how much demand it can tolerate, and how readily it recovers. A treatment may improve function by sustaining compensation or increasing reserve without reversing the process that first disturbed the system.

Fourth, a symptom label must be translated into a testable construct. Apathy, anxiety, pain, sleep disturbance, and autonomic dysfunction can each arise through more than one biological route. Disease, circuit, symptom/construct, and challenge models can all be useful, but they support different claims. The practical sequence used here (meaning, mechanism, model, and measure) keeps the patient problem visible while asking what biology the treatment is intended to alter, which model can test that idea, and which endpoint can distinguish the intended effect from its most plausible alternatives.

Fifth, useful work can begin before a definitive model exists. Using apathy as an example, we show how specific components of goal-directed behavior can be tested while stronger disease-context models are developed. We then compare opportunities across symptom domains and relate them to Atuka’s existing capabilities. Table 4 is a current working view, not a prescription of one model for each symptom. For any program, the choice should depend on the proposed mechanism, evidence of exposure and target engagement, disease stage, and intended clinical claim, and it should change as the evidence and models improve.

The aim is to define the function that matters to patients, identify the circuit or physiological process a therapy is intended to alter, and choose the model and endpoint that can test that claim with the fewest unsupported assumptions.

### Beyond the canonical motor syndrome

Clinical diagnosis of PD continues to require parkinsonism, defined by bradykinesia together with rest tremor and/or rigidity<sup>1</sup>. Reproducing these features has preoccupied much of the preclinical modelling literature. Bradykinesia, rigidity, and tremor are well defined and can be modelled by selective lesioning of the nigrostriatal tract; postural instability can emerge in more extensive or chronic paradigms. Robust L-DOPA responsiveness then provides pharmacological validation of a model's ability to predict symptomatic benefit in patients.

Underlying much of this success is the classic and elegant model of basal ganglia motor circuitry developed over several decades and articulated particularly clearly by Albin, Young, and Penney in 1989<sup>2</sup>. In its classical form, loss of nigrostriatal dopamine changes the balance between the direct and indirect striatal output pathways, increasing inhibitory output from the basal ganglia and restricting thalamocortical and brainstem motor circuits. The model described anatomically connected regions and related neurochemistry into testable predictions about hypokinesia and hyperkinesia and provided a practical framework for understanding why restoring dopaminergic signalling or altering activity within nuclei such as the subthalamic nucleus and internal globus pallidus, can produce marked antiparkinsonian benefit.

What is striking, particularly for many of us who first cut our teeth in PD modelling research 20-30 years ago, is how productive that framework has remained for hypothesis generation despite being incomplete. Nelson and Kreitzer's 2014 reassessment catalogued both the evidence supporting the classical 'rate model' and the observations it cannot readily explain<sup>3</sup>. Mean firing rate alone is insufficient, and more credence is now given to firing patterns, oscillation, synchrony, and pathway co-activation. Even so, findings from 6-OHDA rodent and MPTP-lesioned primates on lesion extent, lesion site, and subsequent dopamine replacement have repeatedly shown that manipulating this circuit has predictable motor consequences. The same framework also provided a useful, if incomplete, way to think about motor complications. Excessive reduction of basal ganglia output is associated with hyperkinetic states, including L-DOPA-induced dyskinesia<sup>3</sup>. In translational terms, this is an important precedent.

A model does not need to reproduce every element of disease biology to be valuable if it captures the circuit abnormality that matters for a given therapeutic question.

The principal limitation of the classical model is one of scope. The basal ganglia themselves are not exclusively concerned with motor output. Associative and limbic corticostriatal loops contribute to cognition, motivation, and affect. But the classical motor circuit was built principally to explain movement disorders arising from altered nigrostriatal dopamine signalling. It is therefore unsurprising that it does not provide an adequate framework for many prodromal and non-canonical features. Apathy, anxiety, sleep disturbance, gastrointestinal dysfunction, or orthostatic hypotension cannot readily be added as further outputs of the same direct-indirect pathway diagram.

Patients commonly live with a wider set of problems. Disturbed sleep, constipation, urinary and cardiovascular dysfunction, cognitive slowing, anxiety, depression, pain, fatigue, and apathy may precede diagnosis or accompany relatively mild motor signs<sup>4-6</sup>. Some are persistent, others fluctuate with dopaminergic state, time of day, or levels of stress. Some are directly related to neurodegeneration, while others are secondary to disability, treatment, reduced activity, or another symptom. The result is a clinical picture in which the burden of PD is not captured well by adding a list of non-motor symptoms to a motor score.

Motor measures tell us what a person achieves, their total output, at a given clinic appointment. They say less about the resources needed to achieve it. Sleep fragmentation, cognitive slowing, apathy, pain, or autonomic instability can add disability directly and can also reduce the reserve available to compensate for motor impairment. Figure 1 is intended to capture this interaction: burden emerges from the symptoms themselves, their timing and treatment state, the context in which a task is attempted, and the effort required to remain functional.

We would not discard the familiar term 'non-motor symptoms'. It is embedded in the clinical literature, in rating scales, and in the language used by patients, clinicians, and funding organizations. It is nevertheless a residual category. Constipation, visual hallucinations, apathy, and orthostatic hypotension have little in common simply because none is a cardinal motor sign. Other features fit poorly on either side of the divide. Freezing of gait is motor in expression but depends on attention, threat, executive

load, and locomotor network dynamics. Speech, swallowing, fatigue, and breathing also bridge the divide.

For that reason, we use 'non-canonical symptoms' when a broader term is helpful. We are not proposing a new clinical classification, the term simply covers symptoms and functional disturbances that fall outside the classical bradykinesia-rigidity-tremor-dyskinesia frame. This can include motor-adjacent phenomena such as freezing and gait instability. The looser term helps keep attention on the translational question instead of on whether a symptom is formally motor or non-motor.

There is also a practical reason to revisit the subject now. Patient-centered studies are placing greater emphasis on problems that affect daily function, while the drug-development environment is beginning to treat selected non-motor symptoms as target indications in their own right. Earlier in 2026 the Michael J. Fox Foundation expanded its Targets to Therapies work to include symptomatic targets and subsequently renamed PPMI as the Parkinson's Precision Medicine Initiative, explicitly reflecting a move away from a one-size-fits-all view of PD<sup>7,8</sup>. Those initiatives do not define a scientific strategy for Atuka, but they are consistent with a field that increasingly needs more precise links between phenotype, biology, and treatment claim.

The patient perspective also changes what counts as progression. In a three-year study of early PD, the reported impact of individual symptoms did not necessarily increase markedly, yet the effort required to maintain usual activities did. Participants became better at coping while ordinary activities became harder to sustain<sup>9,10</sup>. This does not appear to be explained by ageing alone. In the COPPADIS cohort, activities-of-daily-living function declined over two years in 507 people with PD but remained stable in 124 similarly aged controls. The scale used distinguishes normal independence from independence maintained with increasing slowness, difficulty, and effort<sup>11</sup>. Preserved outward performance can therefore conceal a progressive increase in the resources needed to sustain it. For preclinical endpoints, this argues for measuring effort, latency, variability, and failure under load, not only whether performance is ultimately preserved.

# Non—motor and non—canonical features of Parkinson’s disease

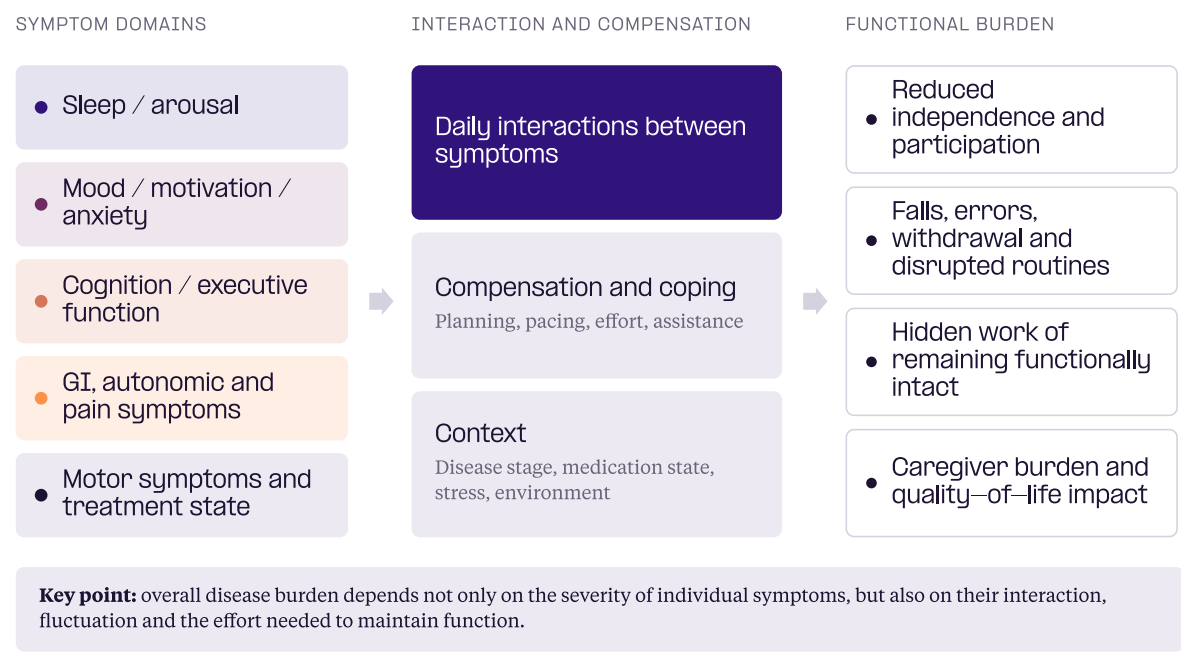


Figure 1. Symptoms interact with compensation and context to determine functional burden

### Symptom architecture and Parkinson's disease heterogeneity

Perhaps we can think about PD as a family of partially overlapping disease processes that converge sufficiently on a recognizable motor syndrome to share a diagnosis. In this way we might separate the common features that define the clinical diagnosis from the richer data set that may carry information about how the disease reached that point.

Recent data complement this view. In 824 newly diagnosed, drug-naive participants from PPMI, Velucci and colleagues identified three subgroups using only REM sleep behavior disorder (RBD), hyposmia, dysautonomia, anxiety, and cognitive impairment. The RBD-positive group had the greatest non-motor burden and a faster subsequent progression to Hoehn and Yahr stage 3 and dementia than the group with minimal non-motor involvement<sup>12</sup>. A smaller 2026 study approached the question from the timing of symptom emergence and again found distinct temporal patterns, influenced strongly by age at onset<sup>13</sup>. While neither study demonstrates that a clinical symptom cluster defines a new PD subtype, both show that the order and co-occurrence of non-motor features contain information that is lost when each symptom is considered independently.

The body-first/brain-first hypothesis of PD origin provides another example. Using probable premotor RBD as a proxy for a body-first phenotype, Velucci and colleagues found a greater premotor burden of hyposmia, cognitive symptoms, pain, constipation, and other dysautonomic features, together with faster progression to Hoehn and Yahr stage 3<sup>14</sup>. This classification remains hypothetical and carries the caveat of RBD being an imperfect proxy for the anatomical origin of alpha-synuclein pathology. It does, however, raise the possibility that symptom profile may provide clues to disease route and timing of disease rather than merely an inventory of patient burden.

Anatomy poses a related problem. A 2026 study used resting-state functional MRI to map connectivity gradients within the human substantia nigra and related them to behavioral measures, neurotransmitter-receptor maps, gene-expression profiles and cerebrospinal-fluid proteomics across four cohorts comprising more than 1,000 participants. A mediolateral gradient was associated more strongly with motor and executive functions, whereas a posteroanterior gradient was related to memory,

anxiety, depression and other cognitive-affective measures<sup>15</sup>. These were gradients, not neatly separable compartments, and therefore not easily interrogated, at least by traditional stereotaxic administration of a particular agent. Indeed, the location and spread of a 6-OHDA or AAV-containing solution will necessarily influence which projections and functions are affected. A model that treats the substantia nigra as a homogeneous dopaminergic reservoir may be entirely adequate for one question and poorly matched to another.

Dopamine contributes to motivation as well as movement, noradrenaline to attention, arousal, stress responses and autonomic regulation, serotonin to mood, anxiety and impulse control and acetylcholine to multiple cognitive and affective domains. Recent human imaging studies have linked depression and anxiety in early PD to overlapping but partially distinct monoaminergic patterns, and broader imaging analyses similarly point to distributed rather than symptom-specific systems<sup>16,17</sup>.

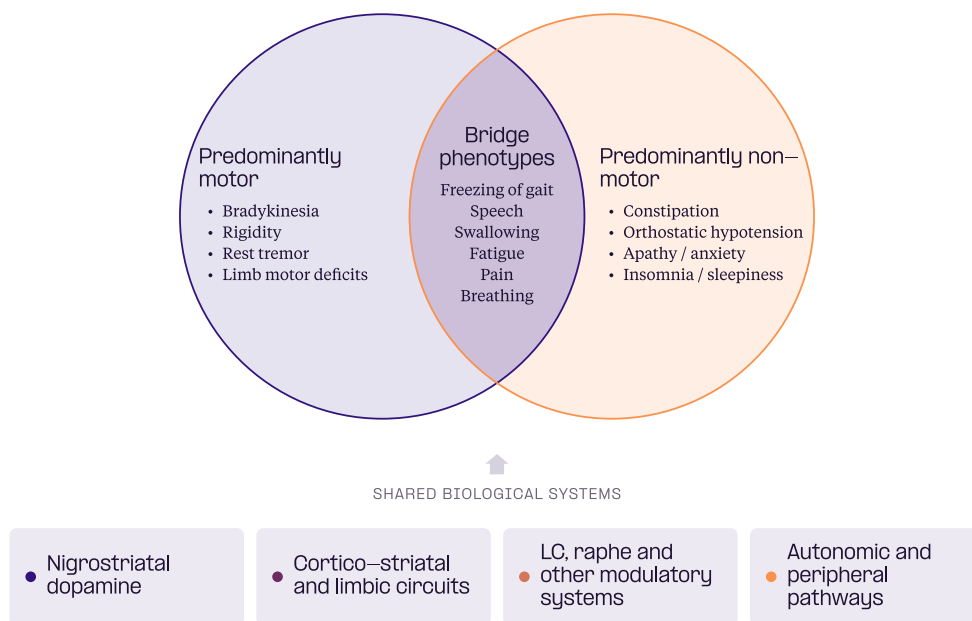


**Figure 2. The divide between motor and non–motor is incomplete**

### Circuits are dynamic. Compensation, reserve, and state transitions

Simplified circuit diagrams are extremely useful, but they can make the underlying biology appear more fixed than it is. Neuronal loss, transmitter depletion, synaptic adaptation, treatment exposure, and changing cortical or subcortical inputs alter circuit state over time. These changes operate on very different scales: seconds during a freezing episode, hours across medication or sleep-wake states, and months or years as pathology and compensation evolve. The same anatomical pathway may therefore support near-normal function in one state and fail under the same demand in another.

This state dependence is especially important for many of the non-canonical features considered here. Apathy, anxiety, cognition, pain, autonomic function, and sleep can fluctuate with context, treatment or demand, making dysfunction easy to miss in a single observation at rest. Translation from animal to patient depends not only on whether the same structure is present, but on whether the circuit is in a comparable state and has comparable compensatory mechanisms available. In experimental models, apparent reserve will also depend on species, strain, sex, and prior experience.

Compensation is not a new concept in PD research but may still be an underused one in model design. Substantial nigrostriatal dysfunction can accumulate before the classical motor symptoms manifest clinically. Proposed mechanisms underlying this include changes in dopamine synthesis, release and turnover, altered receptor and transporter function, and adaptations elsewhere in basal ganglia, cortical and cerebellar circuits<sup>18,19</sup>. The specifics remain debated, particularly in early human disease, but the general principle remains that substantial change to a system often precedes overt functional failure.

Rather than treating the earliest biological change as a threshold, it is more useful to distinguish an accumulating biological phase from two points at which its consequences become visible. During the biological phase, pathology or circuit function has departed measurably from normal but compensation can still preserve output. A functional threshold is crossed when reserve is no longer sufficient to maintain the required behavior or physiological response. A measurement threshold is crossed when a clinical scale, behavioral test, biomarker, or physiological assay becomes sensitive enough to detect the change. These points need not coincide: a coarse scale can make gradual deterioration appear

stepped, while a genuine network transition can occur before the scale detects it.

Freezing of gait illustrates that a real state transition is possible. In people with PD implanted with sensing-capable deep brain stimulation systems, Pozzi and colleagues found that freezing episodes were accompanied by a sudden disruption of cortical-subthalamic coupling. The abnormality persisted during the freeze and resolved when effective walking resumed<sup>20</sup>. Fronto-subthalamic circuitry normally contributes to rapid action stopping<sup>21</sup>, raising the possibility that freezing of gait reflects pathological recruitment or control of an otherwise physiological inhibitory system. Freezing is a specific instance and should not be used as a template for every symptom, but it demonstrates that parkinsonian behavior can depend on rapid changes in network state rather than on a simple monotonic relation between lesion burden and performance.

Two systems may perform similarly at rest while differing greatly in their capacity to tolerate demand. A person with declining cardiovascular reserve may have a normal supine blood pressure but fail during postural challenge. An animal with impaired motivational reserve may collect a freely available reward but stop responding when the effort cost rises. A cognitive deficit may appear only when a task requires switching, divided attention or interference, and a sleep—arousal problem only when sleep is fragmented or arousal thresholds are tested. In each case, the challenge reveals a defect that easy conditions allow the system to conceal.

A treatment need not restore the system by reversing every biological step that produced the abnormal state. A treatment might instead preserve compensation or increase the amount of reserve available before the system fails. In other cases, function may improve because the network finds a different route around the original deficit. Conversely, a severe lesion can make a potentially useful mechanism look ineffective if the model has already removed the substrate through which compensation or plasticity would act.

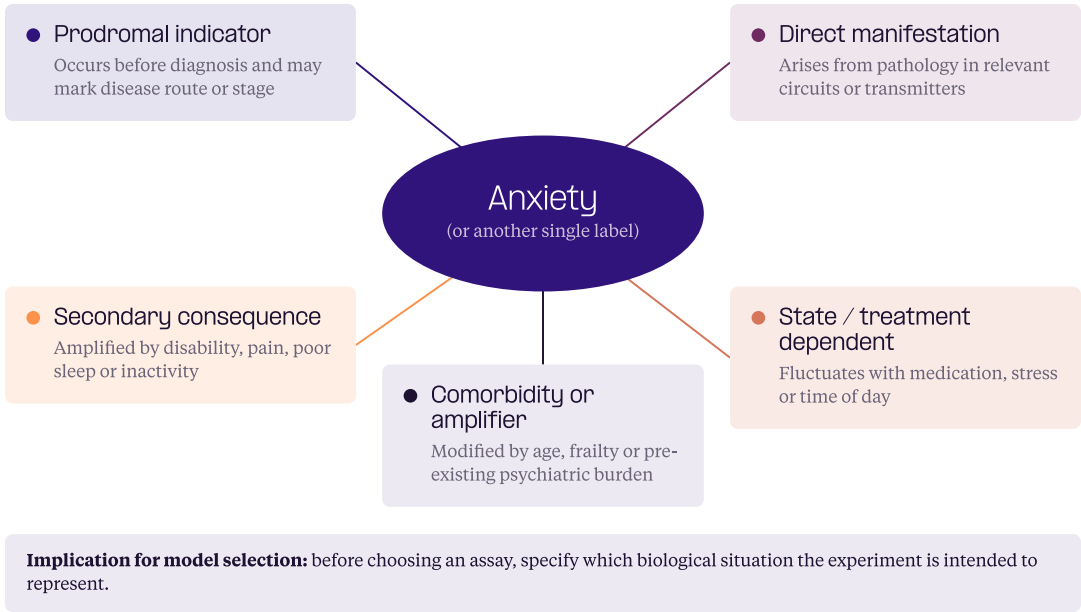
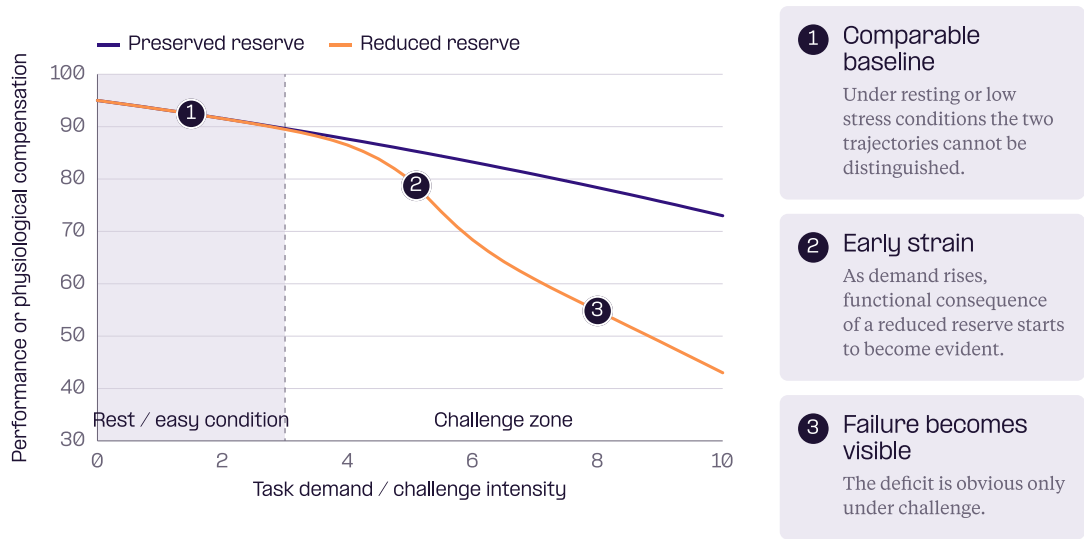


Figure 3. A single symptom label can arise in different biological contexts

# Non–motor and non–canonical features of Parkinson’s disease



**Examples:** progressive-ratio tasks for motivation, set-shifting under higher load, postural challenge for orthostatic control, sleep fragmentation or respiratory stress tests.

Figure 4. Challenge paradigms can reveal reduced functional reserve

Two model animals or PD patients may appear similar under resting conditions but diverge as demand or challenge intensity increases

### A single symptom may arise from a wide range of underlying drivers

The same symptom may manifest as a function of several different and potentially overlapping pathological sources. Anxiety is common in the prodromal phase but can also emerge following the onset of motor symptoms. It may fluctuate during OFF periods, or be secondary to freezing, pain, or increasing social isolation. Pain can be musculoskeletal, dystonic, neuropathic, visceral, or centrally mediated. Sleep disturbance can mean insomnia, REM sleep behavior disorder, fragmented sleep, sleep-disordered breathing, or excessive daytime sleepiness. Apathy may reflect different mixtures of impaired effort allocation, initiation, executive control, and emotional engagement at different disease stages.

A generic model of a symptom is therefore not automatically a model of that symptom in PD. A model of generalized anxiety is not necessarily a useful model of PD-related anxiety. Similarly, a model of reduced movement may not do a perfect job of representing apathy. A PD-specific model is also not always necessary when the therapeutic question concerns a compensatory mechanism that is shared across disease states. A model that cleanly taxes or restores reserve may be more informative than one that reproduces the initiating lesion, provided the same compensatory process is available in PD. A constipation phenotype does not identify whether the relevant defect lies in enteric function, vagal control, sympathetic regulation, diet, hydration, or reduced activity. Face validity is nice to have but can be a weak test when several mechanisms are all able to produce the same outward behaviour.

One useful distinction is between relatively constrained terminal-effector problems and distributed network states. While this distinction is not absolute, it changes the modeling strategy significantly. Sialorrhea and certain aspects of sleep or gastrointestinal function may be interrogated through a defined reflex, end organ or peripheral pathway. By contrast, apathy, anxiety, executive dysfunction, and freezing of gait are more likely to depend on distributed circuits whose behavior changes with context, disease stage and compensation.

Some symptoms sit between the two, with orthostatic hypotension being a good example. Blood-pressure control has a definable physiological output, yet the failure can arise from central autonomic nuclei, peripheral sympathetic denervation, medication,

or their interaction. Gastrointestinal dysfunction likewise has measurable terminal physiology but can be influenced by enteric, vagal, central, and behavioral factors.

Symptoms can also be strongly state-dependent. Non-motor fluctuations involving anxiety, fatigue, pain, and mood are well recognized<sup>22</sup>. A symptom recorded once, at an arbitrary interval following treatment administration, may describe little more than the state present at the time of testing. Longitudinal within-subject designs, explicit pharmacokinetic timing, and continuous home-cage measurements are often more informative. Sleep makes the same point in a different way. A large 2026 clinical dataset showed that RBD, insomnia, and sleep apnoea were associated differently with subsequent multidomain decline, reinforcing the weakness of treating ‘sleep disturbance’ as a single symptom<sup>23</sup>.

Table 1 – Broad categories of translational modelling problems

| Symptom category                                        | Typical examples                                                                                  | Primary modeling question                                                                                                   | Common modeling challenges                                                                          |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Relatively constrained effector or physiological system | Sialorrhea, selected GI or sleep issues                                                           | Can the relevant reflex, organ or pathway be perturbed and measured in a disease-relevant context?                          | Adding broad behavioral interpretation to a narrow physiological phenotype                          |
| Distributed, dynamic network state                      | Apathy, anxiety, executive dysfunction, freezing of gait, certain chronic fatigue and pain states | Which disease-stage-specific circuit state produces the clinical feature, and how does it change under demand or treatment? | Assuming that one assay or one anatomical lesion can capture the whole symptom in all circumstances |
| Mixed problem                                           | GI dysfunction, pain, sleep, breathing, orthostatic hypotension, autonomic symptoms               | Which part of the phenotype is terminal, and which part depends on central state, compensation or context?                  | Treating a composite clinical label as a single mechanism                                           |

### What this changes about model selection

The implications for model selection are relatively straightforward. A model should be judged against the specific therapeutic and translational question rather than against an abstract idea of how completely it resembles PD. This is especially important for non-canonical symptoms, where outwardly similar behaviors may emerge through different, partially overlapping circuit pathways (more a braided river than a direct channel) and where even modest motor impairment can complicate interpretation of behavioral endpoints.

For a disease-modifying programme, upstream biology and progression are central. An alpha-synuclein pre-formed fibril (PFF) or alpha-synuclein overexpression model may be appropriate because the intervention is intended to alter pathology, vulnerability, or spread. For a symptomatic programme, the decisive feature may instead be a disease-relevant circuit state and a clean functional readout. MPTP and 6-OHDA do not reproduce idiopathic PD, yet their ability to model a clinically relevant basal-ganglia state continues to give them exceptional predictive validity for antiparkinsonian or anti-dyskinetic therapeutic development. The same principle can apply outside of the motor system. A simpler model may be translationally useful if it reproduces the appropriate functional process for the intended claim.

Reserve and transition biology can also determine which model is fit for purpose. If a treatment is intended to strengthen compensation, delay a switch into dysfunction, or promote recovery, a model that simply produces a severe endpoint phenotype may have inadvertently removed the biology through which the therapy is expected to act. A more informative design would preserve measurable reserve and ask how much demand the system tolerates before failure, how readily it enters an impaired state and how completely it recovers. In that setting, reserve is not merely a confound or a property exposed by the assay, it is part of the therapeutic hypothesis.

For target-engagement studies, the important feature may simply be that the model produces a biological signal that can also be measured clinically. The ideal readout may be a neurotransmitter measure, electrophysiological signature, imaging marker, cardiovascular response, or digital behavioral feature rather than a specific symptom behavior. The model may therefore be valuable even if it captures only one part of the desired clinical phenotype.

Reviews of non-motor phenotypes in PD models have highlighted substantial inconsistency and weak links between some experimental readouts and the clinical constructs they are said to represent<sup>24</sup>. The 6-OHDA literature, for example, varies markedly in lesion site, severity, lesion extent verification, and behavioral testing approaches<sup>25</sup>. A restricted toxin-based model can be useful, but only if its limitations are built into the study design, not discovered after the result is in.

A better approach is to define the model’s context of use. Instead of stating that a model is ‘validated for apathy’, one might state that a partial bilateral dopaminergic lesion is qualified to detect impaired effort allocation under conditions in which locomotor capacity, reward consumption and task acquisition are preserved. Such narrower statements are perhaps more defensible since they cautiously state what the model can support, what controls are critical, and what might falsify any interpretations.

**Table 2 – Model type and the claim it can reasonably support**

| Model type                | Primary purpose                                                        | Useful when                                                              | Main risk if over-interpreted                                                                                                    |
|---------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Disease model             | Reproduce selected pathology, neurodegeneration or disease progression | The therapeutic mechanism is intended to alter disease biology           | Assuming that every behavioral change is a faithful version of a human symptom                                                   |
| Circuit model             | Perturb a defined nucleus, projection or peripheral pathway            | Causal circuit biology or target engagement is the experimental question | Assuming that a circuit capable of producing the phenotype necessarily reflects the disease process that underlies it clinically |
| Symptom / construct model | Create a defined functional deficit relevant to a clinical outcome     | A symptomatic mechanism requires a clean pharmacodynamic test            | Weak disease relevance if the construct is poorly chosen                                                                         |
| Challenge paradigm        | Expose reduced reserve under controlled demand                         | Dysfunction is compensated at rest or is strongly state-dependent        | Challenge itself dominates the phenotype if it is excessive or non-specific                                                      |

### Translating clinical symptoms into research models

The central difficulty in modeling non-canonical symptoms is that the animal cannot report the experience that defines the clinical condition. An experiment therefore measures a proxy, for instance, willingness to work, avoidance of a threatening environment, memory performance, or perhaps a nociceptive threshold. These measures can be valuable, but only when the construct and any key alternative explanations are described in advance.

Taking apathy as an example, reduced spontaneous movement is compatible with the symptom, but also with bradykinesia, weakness, pain, sedation, anxiety, or sickness. Time spent in the open arms of an elevated-plus maze can reflect threat avoidance, but this depends on locomotion and exploratory drive. A paw-withdrawal threshold can reveal altered nociception without establishing a chronic pain state.

A practical means of helping preserve the clinical question is to consider four steps, meaning, mechanism, model, and measure. 'Meaning' asks what function the patient loses or must work harder to preserve. 'Mechanism' asks which circuit, transmitter system, organ or disease stage is most relevant to that problem and to the proposed therapy. 'Model' asks which perturbation reproduces enough of that biology to test the hypothesis. 'Measure' asks which endpoint is reproducible, challenge-sensitive where appropriate, and protected from the most important confounds. The sequence is deliberately simple and is intended to prevent the common habit of starting with an available model and then searching for symptoms within it.

Challenge-based assays belong principally in the 'measure' step. They are one practical way of interrogating the reserve described earlier, provided that the demand placed on the system resembles the clinical problem.

Where possible, the animal endpoint should also have a recognizable clinical analogue. Wearable device data from PD patients have shown that passive activity and sleep measures can relate to non-motor features, although individual-level prediction remains limited<sup>26</sup>. This argues against collecting generic digital measures for their own sake when what translates best is a matched construct. The closer the functional bridge, the less interpretation is required between the animal result and the clinical question.

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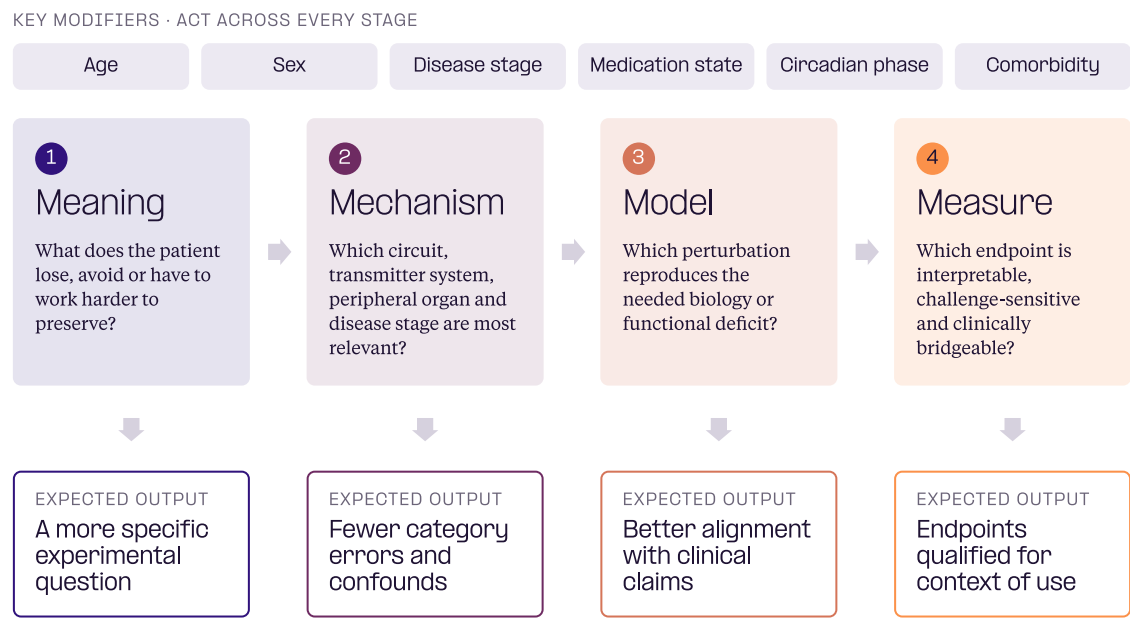


Figure 5. A practical framework for non—canonical symptom study design

Progress is stronger when the patient problem, biology, model choice and readout are specified separately and then reconnected

**Table 3 – From clinical label to measurable construct**

| Clinical symptom        | Candidate construct                                                                | Example readouts                                                                                             | Controls required for interpretation                                        |
|-------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Apathy                  | Effort allocation, reward valuation, initiation, persistence                       | Progressive ratio, effort-based choice, operant initiation latency, voluntary activity under increasing cost | Motor capacity, reward consumption, body weight, sedation, task acquisition |
| Anxiety                 | Threat avoidance, uncertainty, sustained vigilance, state-dependent arousal        | Elevated plus maze, light-dark box, conditioned threat, physiological arousal                                | Locomotion, vision, prior stress, testing order, circadian timing           |
| Executive dysfunction   | Working memory, set shifting, response inhibition, divided attention               | T/Y-maze variants, attentional set shifting, touchscreen or reaction-time paradigms                          | Motor response speed, vision, motivation, task acquisition                  |
| Pain                    | Mechanical/thermal sensitivity, central sensitization, affective-motivational pain | von Frey, thermal assays, grimace, conditioned place paradigms                                               | Motor withdrawal, inflammation, anxiety, analgesic sedation                 |
| Sleep / arousal         | Sleep continuity, REM/NREM architecture, arousal threshold, daytime sleepiness     | EEG/EMG, home-cage video, piezoelectric monitoring, state-transition analysis                                | Circadian phase, handling, sedative effects, housing                        |
| Orthostatic dysfunction | Baroreflex compensation, BP recovery, HR response, cerebral perfusion              | Telemetry during postural challenge, HR variability, vascular responses                                      | Baseline BP, anaesthesia, restraint, hydration, temperature                 |

### Apathy as an example

The topic of apathy in PD has caught our collective imagination. The symptom is clinically important, can occur years before and persist after formal PD diagnosis, is mechanistically heterogeneous, and is easy to misinterpret in an animal model. In PD it is usually defined by a persistent reduction in motivation and goal-directed behavior although that description blends several component parts. Apathy is a reflection of deciding whether a reward is worth pursuing, allocating effort, initiating an action, sustaining the behavior and, finally, integrating cognitive control with value. Apathy overlaps significantly with depression and cognitive impairment whilst retaining its own specific phenotype<sup>27,28</sup>.

Decision-neuroscience approaches have helped make it possible to explore apathy experimentally. In both animals and humans, effort-based tasks ask whether an individual is willing to expend increasing physical or cognitive cost for a valued outcome. In recent human studies, greater apathy has been associated with altered effort-based decision-making and differences in systems supporting goal-directed behavior<sup>29</sup>. While central dopaminergic systems are important, they're not the whole story. A 2026 review of the neurochemistry of effort emphasised interactions between myriad transmitter systems (dopaminergic, serotonergic, noradrenergic, cholinergic and others), providing a plausible basis for clinically similar motivational deficits to arise through a wide variety of biological routes<sup>30</sup>.

The biology of apathy is also unlikely to remain constant as PD progresses. Early motivational apathy in a person with otherwise preserved cognition is likely dominated by a different circuit imbalance from later apathy accompanying executive decline and multisystem pathology. The distinction is not yet sufficiently resolved to define separate clinical entities, but it is a useful modeling hypothesis. It argues for carrying the same behavioral construct across different disease contexts rather than assuming that one lesion or one transmitter manipulation can possibly represent all forms of apathy.

DBS provides an interesting human perturbation experiment. Apathy can increase after subthalamic stimulation, although the effect is difficult to separate completely from medication reduction, stimulation site, and the broader postoperative state<sup>31</sup>. DBS does not offer a simple mechanistic explanation of apathy, but it does show

that changing the state of cortico-basal ganglia circuits can alter motivation independently of a gross motor phenotype.

There may also be an individual reserve component. A person who begins with a strong tendency to pursue effortful rewards may tolerate more degradation of motivational circuitry before inactivity becomes clinically apparent than someone whose baseline choices already favor lower effort and lower risk. This idea might be analogous to cognitive reserve but remains more a hypothesis than clinical dogma. Preclinically, it suggests that baseline choice behavior, response vigor and the slope of performance across increasing effort may be more informative than a single endpoint measured following a lesion.

### A recent construct—led program: tetrabenazine and AB—300

The AB-300 program runs counter to the assumption that the most disease-like animal model must always be the most translational. Tetrabenazine inhibits VMAT2 and can produce a reversible reduction in effortful responding. Savchenko and colleagues reported that low-dose tetrabenazine reduced progressive-ratio performance in rats while preserving simpler measures of reinforcer value and gross locomotion, supporting its use as a model of reduced willingness to work rather than of general motor suppression<sup>32</sup>.

In September 2026, Ariadne Bio announced that AB-300, a non-hallucinogenic serotonin 2A (5-HT<sub>2A</sub>) receptor agonist, is being advanced for apathy in PD. The company reported that, in a tetrabenazine-induced motivational-deficit model assessed by progressive-ratio lever pressing, AB-300 plus tetrabenazine increased motivational behavior by 89% relative to the tetrabenazine-vehicle control group<sup>33</sup>. The result is company-reported and has not yet been described in a peer-reviewed efficacy paper. The Phase 1b trial, expected to begin in the second half of 2026, is funded in part through the Michael J. Fox Foundation's Therapeutics Pipeline Program and is intended to test safety, exposure, and an apathy signal in people with PD.

The translational interest lies in the logic of the program. The tetrabenazine model clearly does not resemble PD pathology. The model creates a defined motivational deficit, the assay measures an explicit component of motivated behavior, and the clinical development plan targets apathy. If AB-300 succeeds clinically, the

program will provide a striking example of a construct-led route from animal behavior to a PD trial. If it fails, the experiment will still test the assumptions linking the construct, pharmacology, and clinical symptom.

IRLAB's linepemat program makes the same broader point from a different pharmacological starting position. Linepemat (IRL757) entered the LIFT-PD Phase 1b study in February 2026, with recruitment continuing through the year and initial results expected in 2027<sup>34</sup>. IRL757 is a nootropic agent whose efficacy is thought to be linked to an ability to influence cortical-to-subcortical signalling. Its preclinical development strategy differs from that of AB-300, suggesting that the field is exploring more than one biological route into a common clinical phenotype.

### Implications for an Atuka apathy platform

For Atuka, a staged approach is more useful than declaring any one model to be 'the' apathy model. A pharmacological construct model can qualify effort-based assays and comparator pharmacology. A bilateral low-dose nigral 6-OHDA lesion can then ask whether the same construct is impaired in a stable parkinsonian context while gross motor ability remains sufficient for testing. Chronic low-dose MPTP paradigms in NHP and circuit-targeted alpha-synuclein approaches provide other opportunities to examine executive-motivational interactions and synaptic dysfunction.

Once the constructs and their principal confounds are understood in rodents, an NHP stage may provide a closer translational bridge through analogous effort-based or decision-making tasks, particularly for compounds moving towards early clinical proof of concept.

This approach also creates useful negative controls. If a treatment increases open-field activity but leaves progressive-ratio performance unchanged, increased locomotion should not be described as reversal of apathy. If progressive-ratio responding improves while reward consumption falls or motor capacity changes, the interpretation is equally uncertain. A strong apathy package should be designed so that the simplest alternative explanation can be rejected, not merely so that one endpoint reaches statistical significance.

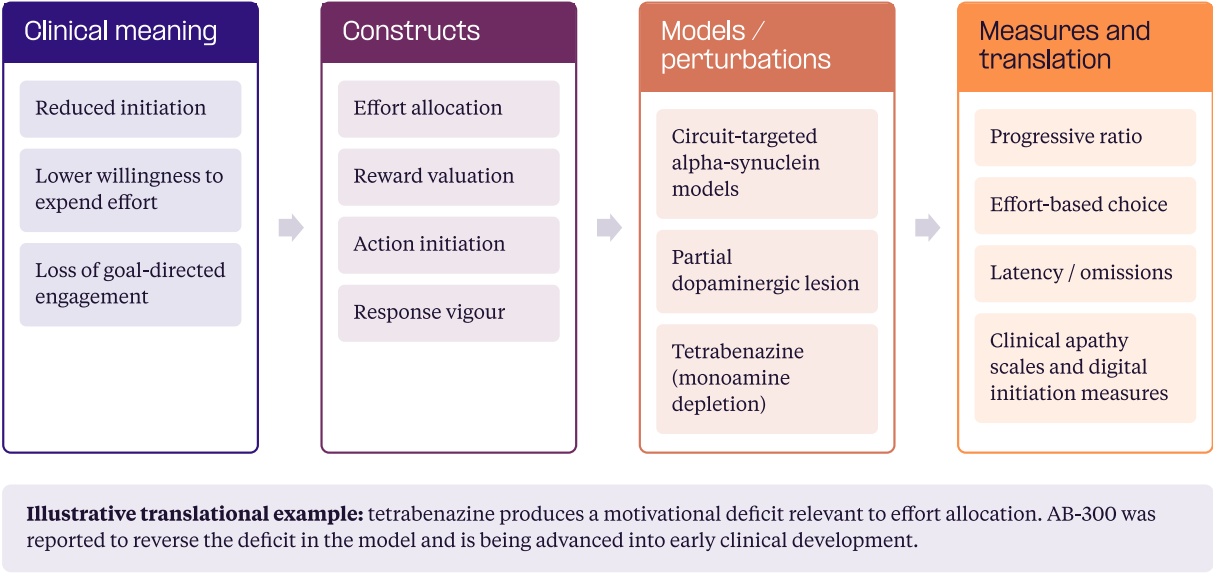


Figure 6. A construct–led translational path for apathy

### Applying the approach across symptom domains

The useful distinction across symptom domains is not simply how quickly an assay can be established, but how directly an animal readout maps onto the clinical phenomenon and how much confidence exists that a treatment effect will translate. Dyskinesia in the MPTP NHP lies near one end of that spectrum. The behaviour is clinically recognizable, and the model has a substantial and largely successful translational record<sup>35,36</sup>. Effort allocation or threat avoidance lies further away. Each measures one component of apathy or anxiety, but neither alone establishes the whole clinical syndrome. Some domains therefore offer a relatively direct route to a clinically interpretable efficacy signal, whereas others require confidence to be built progressively across constructs, controls, disease contexts, and species. The sections below consider where each domain currently sits along that path.

### Anxiety and affective state

Anxiety in PD can be trait-like, situational, medication-state dependent or secondary to other problems. As with apathy, it can appear early in the prodromal phase, can be extremely debilitating, and is often hard to attribute to an underlying, developing parkinsonism. It can interact with freezing of gait, but association does not establish a simple causal chain. In a 2026 randomised study of people with PD and anxiety-related freezing, a behavioral intervention directed at anxiety did not significantly reduce objectively measured freezing compared with a wait-list control<sup>37</sup>. The result suggests a need to guard against treating two correlated symptoms (in this case anxiety and freezing of gait) as interchangeable therapeutic targets.

Atuka already uses open-field arena and elevated-plus-maze endpoints in rodent assays as well as the human-intruder test in non-human primates. In MPTP-lesioned macaques, alprazolam reduced Human Intruder Test anxiety scores at doses selected in advance because they produced no observable sedation (Figure 7D). Future development will place less weight on any single avoidance measure and more on convergent behavior, physiological arousal, and state dependence. Motor capacity must be quantified explicitly in parkinsonian models. Circuit-targeted work involving locus

coeruleus, amygdala, cortex, and their interactions with striatal systems offer a route to stronger construct validity.

### Cognition and executive function

Cognitive impairment is the clearest case for the demand-based approach described earlier. Atuka's decades of experience with the chronic low-dose MPTP macaque model are relevant because cognitive dysfunction can precede severe motor impairment. In that model, macaques trained to stably perform a simple discrimination and reversal task develop a deficit of at least 15% that persists for at least three months while motor impairment remains minimal. The deficit is also pharmacologically sensitive and can be reversed (Figure 7C)<sup>38</sup>. The ideal translational route is to separate task acquisition and response speed from the executive operation of interest, then increase load until the deficit is exposed. This also provides a way to study compensation directly. The point at which performance begins to fail can be more informative than a single score under one task condition.

### Freezing of gait and motor—adjacent states

Freezing of gait sits awkwardly within a motor/non-motor classification. While freezing of gait is clearly a motor phenomenon, its expression is influenced by attention, anxiety, visual information, executive control, and locomotor network dynamics. Human electrophysiology studies suggest that a freezing episode can be initiated by a network transition rather than simply a worsening of bradykinesia<sup>20</sup>. Preclinical models that could reproduce this type of episodic switching and the conditions that precipitate it could better capture the complexity of the symptom beyond mere slowing of activity.

### Orthostatic hypotension and autonomic failure

Orthostatic hypotension is a contrasting case because the physiological output is well defined. Recent clinical work nevertheless shows that objective haemodynamic abnormalities and subjective symptoms do not map neatly onto one another<sup>39,40</sup>. A preclinical study would ideally measure both the regulatory failure and its functional consequences where possible. Continuous measures are also preferable, and telemetry would provide a far

richer picture during a reproducible postural or gravitational challenge than a single resting or anaesthetised blood-pressure measurement.

A model based on alpha-synuclein pathology in medullary autonomic nuclei or peripheral sympathetic pathways could start to address prodromal synucleinopathy, whereas a pharmacological baroreflex model may be better for screening a symptomatic mechanism. Both can be useful; the choice is determined by the question under study.

### Sleep and arousal

Sleep requires decomposition before it can be modeled. REM sleep behavior disorder, insomnia, sleep fragmentation, and excessive daytime sleepiness are different phenomena with different mechanisms and clinical implications<sup>23</sup>. Even basic assessments of home-cage activity demonstrate the problem. MPTP-lesioned macaques show almost twice their pre-MPTP night-time home-cage activity (Figure 7B), but actigraphy alone cannot determine which sleep or arousal process is responsible and EEG/EMG telemetry is the logical next step. Alpha-synuclein PFF targeting of the sublateralodorsal tegmental nucleus in mice has produced RBD-like sleep abnormalities in advance of phenoconversion to motor, affective, olfactory and gastrointestinal changes<sup>41</sup>. Such models are particularly attractive when disease progression and spread are part of the question. By contrast, a symptomatic insomnia study may require a simpler endpoint package centred on sleep continuity, arousal thresholds and next-day function. Sleep assessment may be especially sensitive to species and strain. Rodents are nocturnal and sleep in multiple bouts, and commonly used C57BL/6J mice are deficient in endogenous melatonin synthesis<sup>42</sup>. Circadian phase, strain, and the biology of the chosen species are therefore part of the model rather than merely husbandry variables.

### Pain

Pain in PD includes musculoskeletal, dystonic, neuropathic, visceral, and centrally mediated components. Mechanical and thermal thresholds are experimentally tractable, but a change in withdrawal response is not equivalent to a chronic pain state. Existing toxin models primarily reproduce altered nociceptive

sensitivity, although they can also be used to interrogate the circuits responsible<sup>43</sup>. In the unilateral 6-OHDA rat, for example, mechanical hypersensitivity has been linked to abnormalities in descending pain-modulatory pathways involving the periaqueductal grey, raphé magnus, and spinal dorsal horn, with related pathology identified in human PD tissue<sup>44</sup>. A useful development programme should therefore combine evoked measures with spontaneous or affective readouts and establish whether the phenotype depends on medication state, locomotor impairment, or inflammatory change. The clinical pain subtype should be specified before the model is selected.

### Gastrointestinal dysfunction and brain—body regulation

Gastrointestinal dysfunction has both practical and biological importance. Atuka and collaborators have shown that alpha-synuclein expression in vagal motoneurons can alter pacemaking and gastrointestinal motility (Figure 7A)<sup>45</sup>. Other studies have demonstrated brain-to-gut trafficking of alpha-synuclein through immune-cell pathways<sup>46</sup>. These studies make clear that relevant PD biology can lie outside of the nigrostriatal system and may not be captured by a CNS-restricted model. The site of the GI dysfunction also matters. Pellet output, gastric emptying, colonic transit, and swallowing measure different parts of the system.

These domains may also intersect through the brain’s regulation of internal bodily state. Evidence for altered brain-heart coupling in PD is still preliminary, but it points toward a useful class of translational endpoints in which central network state and peripheral physiology are measured together<sup>47</sup>.

Table 4 summarizes our current working view of what can be interrogated usefully now and where further endpoint or model development is needed. It is not a menu of fixed recommendations, nor a prescription of one model for each symptom. For a particular therapy, the preceding framework should still be applied to its mechanism, evidence of exposure and target engagement, relevant disease stage, and intended clinical claim. The table should change as endpoints are qualified, new models are developed, and clinical studies clarify which constructs matter.

## Non–motor and non–canonical features of Parkinson's disease

**Table 4 – Candidate development priorities viewed through a circuit–state lens**

| Domain                      | Predominant problem                                        | Disease-stage question                                                   | Near-term model / endpoint                                                              | Longer-term opportunity                                                                                                            |
|-----------------------------|------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Apathy                      | Distributed motivational state                             | Does early effort-allocation failure differ from later cognitive apathy? | Progressive ratio and effort-based choice with explicit motor and consummatory controls | Carry common constructs into partial bilateral DA lesions, chronic low-dose MPTP, circuit-targeted alpha-synuclein and NHP studies |
| Anxiety                     | Distributed affective state                                | Trait, prodromal, OFF-state or secondary anxiety?                        | Convergent avoidance plus physiological arousal with locomotor controls                 | LC/amygdala/cortical circuit models; threat under cognitive or gait challenge                                                      |
| Executive dysfunction       | Distributed cognitive state                                | Which operation fails first as demand rises?                             | Set shifting, working memory and attentional load with response-speed controls          | Longitudinal corticostriatal physiology and clinically mirrored digital endpoints                                                  |
| Freezing / gait instability | Motor-adjacent transition state                            | Is the problem slow gait, network switching or failure under conflict?   | Demand- and conflict-sensitive locomotor paradigms                                      | Circuit-state readouts spanning cortex, STN/PPN and basal ganglia                                                                  |
| Orthostatic hypotension     | Autonomic effector plus central/peripheral disease context | Is dysfunction central, peripheral or combined?                          | Telemetry during standardised postural challenge; BP/HR recovery                        | Synuclein models involving medullary and peripheral autonomic pathways                                                             |
| Sleep / arousal             | State-transition and physiological control                 | RBD, insomnia, fragmentation or daytime sleepiness?                      | Longitudinal sleep continuity and state-transition measures                             | Circuit-specific synuclein models; EEG/EMG and home-cage translation                                                               |
| Pain                        | Mixed sensory and affective state                          | Persistent central sensitization or state-dependent pain?                | Mechanical/thermal plus spontaneous or affective readout                                | Map PD pain subtypes to medication state and circuit pathology                                                                     |
| GI dysfunction              | Peripheral/brain-body system                               | Which segment and regulatory pathway fails, and when?                    | Segment-specific motility, emptying or transit measures                                 | Longitudinal enteric/vagal synuclein models and brain-gut biomarkers                                                               |

### Atuka's existing foundation and development priorities

Atuka scientists have worked for many years with toxin, alpha-synuclein, and genetic models of PD in rodents and non-human primates. Together with behavioral, neurochemical, and neuropathological endpoints, several strands of that work already sit squarely within the non-canonical space.

The clearest published example is gastrointestinal biology. Chiu and colleagues showed that A53T alpha-synuclein expression in vagal motoneurons produced a Kv4 channelopathy, impaired pacemaking, and gastrointestinal dysmotility in mice<sup>45</sup>. Brain-to-gut trafficking studies provide a complementary example of pathology moving through central, peripheral, and immune compartments<sup>46</sup>. Cognitive programs are long-established with Atuka studies having used rodent and particularly non-human-primate PD models to examine cognition and attention, including pharmacological manipulation of dopamine and norepinephrine systems<sup>48</sup>. Figure 7 brings together four in-house datasets, first presented at SfN in 2024<sup>49</sup>, each pairing a construct from Table 3 with a control that makes it interpretable. Whole-gut transit after vagal alpha-synuclein expression, night-time activity after MPTP, reversal learning after chronic low-dose MPTP with minimal motor impairment, and Human Intruder Test anxiety at non-sedating anxiolytic doses. None is offered as a complete model of the corresponding symptom but together they show where our current capability sits and what each dataset can and cannot address.

## Non-motor and non-canonical features of Parkinson's disease

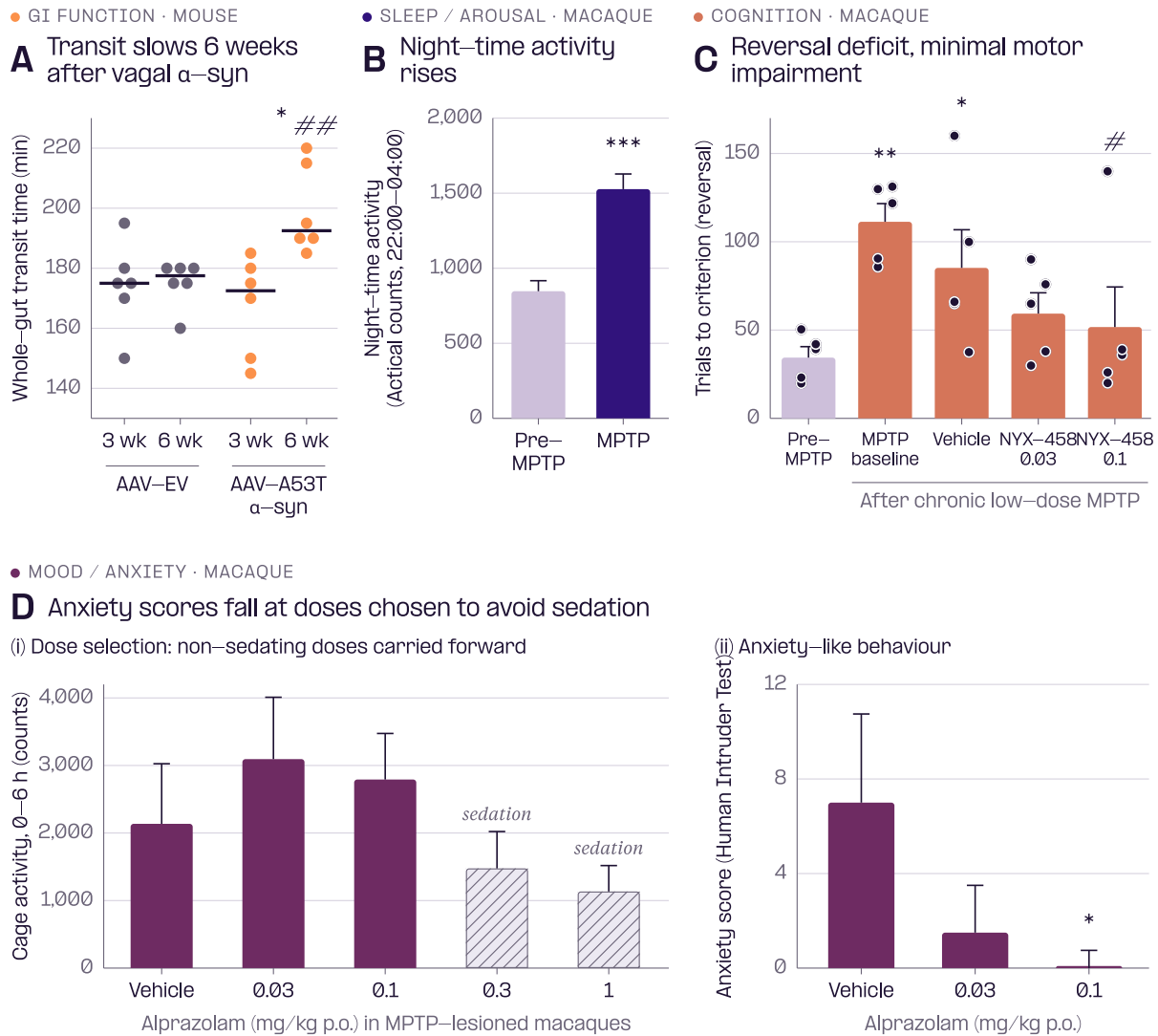


**Figure 7. Atuka in-house data across four non-motor domains**

(A) Whole-gut transit time (carmine red) 3 and 6 weeks after cervical vagal injection of AAV1/2-hA53T- $\alpha$ -synuclein or empty vector (EV) in male C57BL/6J mice; individual mice with median. \*  $P < 0.05$  vs  $\alpha$ -synuclein 3 weeks; ##  $P < 0.01$  vs EV 6 weeks (one-way ANOVA)<sup>45</sup>. (B) Night-time home-cage activity (Actual counts, 22:00–04:00) in female cynomolgus macaques before and after MPTP; mean  $\pm$  SEM. \*\*\*  $P < 0.001$  (unpaired t-test). (C) Trials to criterion on a simple discrimination and reversal task in male cynomolgus macaques before and after chronic low-dose MPTP, and after acute NYX-458 (0.03 and 0.1 mg/kg p.o.); mean  $\pm$  SEM with individual animals. \*\*  $P < 0.01$ , \*  $P < 0.05$  vs pre-MPTP; #  $P < 0.05$  vs vehicle (one-way repeated-measures ANOVA, Fisher's LSD)<sup>46</sup>. (D) Alprazolam (p.o.) in MPTP-lesioned female cynomolgus macaques: (i) observation-cage activity over 0–6 h, mean  $\pm$  SEM, with sedation scored from video by a blinded observer; (ii) Human Intruder Test anxiety scores at the two non-sedating doses, median and upper quartile. \*  $P < 0.05$  vs vehicle (Friedman test, Dunn's post hoc). Redrawn from Johnston et al., SFN 2024<sup>40</sup>.

Circuit-targeted alpha-synuclein models provide further examples. Selective alpha-synuclein overexpression in the locus coeruleus can produce pathological, glial, and electrophysiological changes relevant to prodromal disease<sup>50-52</sup>, while intrastriatal oligomeric alpha-synuclein has been reported to alter corticostriatal plasticity and anxiety-like behavior before marked nigral cell loss<sup>53</sup>.

Endpoint qualification in a relatively clean model will often be the most useful first step. That approach avoids the ethical, logistical, and cost issues of running a PD animal model experiment with an endpoint whose confounds have not been resolved first. Conversely, a symptom assay should not be allowed to remain permanently detached from disease biology if the ultimate claim depends on PD-specific circuitry.

The internal distinction between terminal-effector problems and distributed states is helpful for prioritization. Atuka's historical strengths in circuit biology, behavior, and translational study design are particularly relevant to state-dependent problems such as apathy, anxiety, and executive dysfunction. More constrained physiological problems such as orthostatic hypotension or selected gastrointestinal outputs are also attractive when there is a strong disease-relevant mechanism and a clear bridge to the clinic. The criterion should not be whether a symptom appears high on an external priority list, but whether Atuka can define a sharper biological question and a defensible experimental path.

The approach extends the model-selection principles described in Atuka's earlier White Papers. Model choice should follow indication, mechanism, therapeutic modality, development stage, pharmacokinetics, and endpoint strategy rather than convention<sup>54</sup>. The newer biological-classification perspective adds that PD itself is heterogeneous and increasingly likely to be stratified by biology rather than treated as one uniform entity<sup>55</sup>. The present paper seeks to add to these conversations and extend both ideas into the symptom domain with the patient problem, the disease route, and the circuit state remaining visible throughout study design.

### Conclusions

Non-motor and non-canonical symptoms are increasingly treated as therapeutic targets in their own right, and the preclinical models used to study them need to keep pace. We don't think a single model or framework will solve this but have tried to offer a means of approaching it. Start from the patient problem, consider which circuit or effector is likely to be involved at a given disease stage, and choose a model and endpoint capable of testing that idea.

Describing a model by what it can reasonably support (an effort-allocation deficit with motor capacity controlled, for example) is more modest than calling it a model of apathy, but it is easier to defend and more helpful to a collaborator deciding on next steps.

Many of these symptoms are also likely to be compensated for long periods, in animals as in patients. Baseline measures taken before a lesion or seeding event, and testing under graded demand, will therefore often tell us more than a single endpoint recorded at rest.

In the near term, a sensible place to start is a small number of areas where construct, assay, and clinical interest are reasonably well aligned. Apathy is one. Orthostatic hypotension, where the physiology is measurable and the clinical definition already includes a challenge, may be another. Other domains will take longer, and some will be best approached through collaboration.

Finally, if the pattern and timing of non-motor symptoms do reflect differences in underlying disease, modeling them carefully may help with the heterogeneity problem as well as with the burden these symptoms place on patients.

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## About the Authors



**Dr Tom Johnston** serves as Atuka's Chief Scientific Officer. His research focuses on translating advances in fundamental science into new therapeutic strategies for Parkinson's disease (PD) and related neurodegenerative conditions. He has helped develop, refine and implement a wide range of rodent and non-human primate models of PD to support the evaluation and clinical development of promising therapies. His early work helped identify several non-dopaminergic approaches for the symptomatic treatment of PD and L-DOPA-induced dyskinesia, a major complication of long-term L-DOPA treatment. More recently, his work has focused on  $\alpha$ -synuclein-based models and the assessment of therapies with the potential to modify disease progression. He and his colleagues at Atuka have also expanded their research into the non-motor and non-canonical symptoms of PD, including approaches to modelling these symptoms and evaluating potential treatments. Tom has authored more than 60 original research articles, reviews and book chapters. His work has been cited more than 3,500 times, and he has an h-index of 39.



## A cure for Parkinson's, faster, through the world's best preclinical neuroscience.

**Atuka's lead scientists have dedicated their careers to furthering our understanding of Parkinson's disease, advancing novel therapeutics, and alleviating the burden of those suffering from neurological disorders.**

For more than 20 years, we have collaborated with our partners to provide preclinical services that expand the frontiers of Parkinson's disease research, and help make new, life-changing therapeutics a reality. Our neuroscientists have extensive preclinical experience developing therapies for numerous indications—including Parkinson's, cognitive disorders, Alzheimer's, ALS and other movement disorders such as dystonia and dyskinesia—across multiple modalities, including small molecules and biologics.

Founded by Dr. Jonathan Brotchie in 2003, Atuka has been involved in the preclinical evaluation of more than 300 potential therapeutics, predominantly in Parkinson's disease, of which more than 30 have progressed to clinical trials—a level of experience without equal in our field globally.

Our lead scientists have collectively published more than 300 peer-reviewed, highly-cited papers, and individually possess h-indices ranging from 25 to 83.

Atuka has collaborated with over 90 organizations, including large pharmaceutical and biotech companies, charitable foundations, universities, and government agencies. Over the course of more than 400 preclinical projects, targeting more than 60 mechanisms of action, we have built an extremely rich understanding of Parkinson's disease, its causes, and potential treatments.

With offices and facilities in Toronto and Suzhou, our team is diverse both in background and expertise, bringing to every one of our partner engagements a spirit of close collaboration, along with a commitment to the highest ethical standards in scientific research.