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Peer Review

Review of: "A Novel Exercise Template for Parkinson's Based on Energetic Dynamics"

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This commentary presents an original "energetic-dynamics" framework for understanding moment-to-moment motor variability in Parkinson's disease. The author proposes that unstable mitochondrial ATP production may contribute to fluctuations in movement performance even when dopaminergic medication or deep brain stimulation provides adequate motor signalling. On this basis, the manuscript interprets the apparent benefits of tango as arising partly from its alternating structure of short rhythmic movement bouts and brief recovery periods and proposes a home-based programme of seated, rhythmically cued intervals, potentially supplemented by meditation.

The manuscript is engaging, accessible, and imaginative. Its attempt to connect mitochondrial dysfunction, acute exercise responses, rhythmic cueing, fatigue, and symptom variability is potentially thought-provoking. The proposed intervention is also simple, inexpensive, adaptable, and empirically testable. The article therefore has value as a hypothesis-generating commentary.

However, the current version repeatedly moves from biological plausibility to mechanistic certainty and then to clinical prescription without sufficient direct evidence. Established findings, mechanistic inference, and speculation are not consistently distinguished. Several central claims are supported only indirectly, and some statements regarding exercise, neural circuitry, ATP availability, and possible disease modification substantially exceed what can be concluded from the cited literature.

The commentary would be considerably strengthened by reframing the energetic-dynamics model as one possible complementary hypothesis, not as an explanation that displaces established mechanisms of Parkinsonian motor dysfunction or existing rehabilitation principles.

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Major comments

1. The manuscript should distinguish established evidence from hypothesis and speculation.

The central difficulty is not that the proposed model is speculative; hypothesis papers and commentaries can legitimately present speculative ideas. The difficulty is that the manuscript frequently presents inferred mechanisms as though they were established.

For example, mitochondrial dysfunction is well recognised in Parkinson's disease, and neural activity is dependent on adequate cellular energy. These observations make the proposed hypothesis biologically plausible. They do not, however, establish that transient fluctuations in mitochondrial ATP production are responsible for moment-to-moment changes in gait, freezing, rigidity, handwriting, responsiveness to cueing, or the effects of deep brain stimulation.

Throughout the manuscript, the author should clearly label statements according to their evidential status:

- established evidence;
- plausible mechanistic interpretation;
- prediction of the proposed model;
- clinical speculation requiring direct testing.

Phrases such as "this naturally explains," "this helps explain," "the real limitation is energetic fragility," and "it is evidence that they were never adequately powered" often imply that competing explanations have been excluded when they have not.

A more appropriate formulation would be:

"The energetic-dynamics framework offers a testable complementary hypothesis that may contribute to some forms of short-term motor variability."

This would preserve the novelty of the commentary while avoiding unwarranted mechanistic certainty.

2. The proposed causal chain is not directly demonstrated.

The manuscript effectively proposes the following chain:

1. Parkinson's disease involves mitochondrial dysfunction;
2. mitochondrial dysfunction causes unstable moment-to-moment ATP availability;

3. unstable ATP availability limits basal ganglia motor processing;
4. short exercise intervals acutely increase ATP availability;
5. this acute increase improves movement;
6. brief recovery periods prevent energetic depletion;
7. repeated sessions may support neuronal maintenance and potentially slow disease progression.

Each component is individually plausible to varying degrees, but the complete chain has not been demonstrated in people with Parkinson's disease. In particular, the cited acute exercise study concerns skeletal-muscle mitochondrial ATP production and does not establish rapid increases in ATP availability within basal ganglia networks or dopaminergic neurons following rhythmic seated movement. The manuscript currently extrapolates across tissue, population, exercise mode, and outcome.

The author should explicitly acknowledge these translational steps. Evidence regarding skeletal-muscle bioenergetics should not be treated as direct evidence of central nervous system ATP dynamics.

3. The interpretation of tango's effectiveness is insufficiently supported.

The commentary argues that tango may be especially effective because its traditional structure consists of approximately three-minute dances separated by one-minute recovery periods. This is an interesting hypothesis, but the available evidence does not establish that this interval pattern is the active therapeutic component.

Tango interventions in Parkinson's disease differ considerably in class structure, intensity, duration, instructional approach, partner involvement, music, progression, and choreography. Moreover, the cited Cochrane review does not demonstrate that tango is uniquely or consistently superior because of its energetic structure. Network meta-analytic rankings should also be interpreted cautiously, particularly when comparisons are indirect, interventions are heterogeneous, and certainty of evidence varies.

The manuscript should recognise that the effects of tango may arise through several interacting mechanisms, including:

- rhythmic auditory cueing;
- external movement initiation;
- attentional strategies;
- repeated practice of turning and multidirectional stepping;
- balance challenges;

- amplitude and weight-shifting practice;
- motor learning;
- partner interaction;
- motivation, enjoyment, and adherence;
- social participation.

The energetic explanation could be presented as an additional, currently untested mechanism rather than as the mechanism that "makes tango effective."

4. Acute improvements do not exclude motor learning or neuroplastic mechanisms.

The manuscript argues that improvements observed within a single class are more consistent with rapid increases in cellular energy than with neural retraining because structural neuroplastic processes require longer periods. This creates an overly narrow distinction.

Immediate performance changes do not require structural synaptic remodelling. They may reflect acute cueing, attentional compensation, altered movement strategy, arousal, changes in motor-set preparation, practice effects, improved confidence, reduced fear, or short-term functional changes within existing networks. Acute performance enhancement and longer-term motor learning are not mutually exclusive.

The manuscript should avoid presenting ATP availability and neural mechanisms as competing explanations. A more defensible proposal would be that energetic state might modulate the ability of existing neural networks to respond to cueing and practice.

5. The neurophysiological description is at times oversimplified or inaccurate.

Several descriptions of basal ganglia function require revision. Statements such as "dopamine provides the instruction that allows a movement to begin" substantially simplify dopaminergic modulation and basal ganglia circuitry. Similarly, the suggestion that the basal ganglia "must supply the energetic resources" for motor-control signals is conceptually unclear. The basal ganglia require metabolic energy to function, but they do not supply ATP to motor circuits in the manner implied.

The analogy between ATP availability and electrical "voltage" may be accessible to general readers but risks being physiologically misleading. ATP concentration, ATP turnover, mitochondrial membrane potential, energy demand, and neural signalling are related but distinct concepts.

The author should consult or cite more specialised literature on:

- basal ganglia physiology;
- cerebral energy metabolism;
- neuronal versus skeletal-muscle mitochondrial responses;
- central fatigue;
- neural mechanisms of freezing of gait;
- compensatory effects of external cueing.

The proposed model should be built on more precise neurophysiological terminology.

6. The account of Parkinson's rehabilitation and stroke rehabilitation is overly reductive.

The manuscript states that much Parkinson's rehabilitation has been modelled on stroke recovery and suggests that Parkinsonian motor circuits remain intact whereas stroke destroys circuits that must be rebuilt. This comparison is too categorical.

Both disorders are heterogeneous. Stroke may disrupt particular networks without completely destroying motor representations, while Parkinson's disease affects distributed motor, cognitive, sensory, and limbic networks and is not simply a condition in which intact motor programmes lack sufficient ATP for retrieval. Contemporary Parkinson's rehabilitation is not based solely on a "stroke-style retraining model." It includes cueing, strategy training, amplitude-based exercise, aerobic conditioning, resistance training, balance training, dual-task training, task-specific practice, dance, and behavioural approaches.

The manuscript should either remove this comparison or revise it substantially. The energetic hypothesis does not require existing rehabilitation approaches to be portrayed as biologically misguided.

7. The proposed exercise dose is arbitrary at present.

The recommended structure of four approximately three-minute intervals separated by one-minute rests appears to be derived primarily from the organisation of tango tandas and cortinas. This does not establish an optimal physiological dose.

The author should clarify that the proposed 15-minute structure is a starting hypothesis rather than an evidence-based prescription. The manuscript should discuss potentially relevant variables such as:

- exercise intensity;
- heart-rate or perceived-exertion targets;
- medication state;

- disease stage;
- autonomic dysfunction;
- fatigue;
- orthostatic hypotension;
- cardiovascular comorbidity;
- cognitive impairment;
- dyskinesia;
- baseline physical activity;
- progression and individualisation.

Without intensity specification, three minutes of seated movement could represent a negligible stimulus for one person and an unsustainable workload for another.

8. The proposed exclusive or preferential use of seated exercise requires caution.

Chair-based exercise may improve accessibility and safety for some people with advanced balance problems, fatigue, or freezing. However, Parkinson's disease commonly requires direct training of gait, transfers, postural transitions, reactive balance, lower-limb strength, and standing tolerance. A seated intervention cannot be assumed to reproduce the therapeutic demands of tango or substitute for ambulatory and balance exercise.

The commentary should present seated intervals as one accessible option, particularly for selected individuals, rather than as a generally preferable model. It should also state that exercise prescription should be individualised and that people at increased risk should receive assessment or supervision from an appropriately qualified healthcare or exercise professional.

The statement that seated exercise "eliminates" fall risk or other barriers should be moderated. It may reduce some risks and logistical demands but does not eliminate all safety concerns.

9. Claims that conventional exercise may "defeat the purpose" are not adequately balanced.

The manuscript argues that 30- or 45-minute aerobic, treadmill, or cycling sessions may exhaust people with compromised mitochondrial function and potentially stress the very system they are intended to support. Some individuals with Parkinson's disease undoubtedly experience post-exertional fatigue or difficulty tolerating prolonged sessions. However, this does not justify a broad critique of standard exercise models.

There is substantial evidence supporting appropriately prescribed aerobic, resistance, balance, gait, and multimodal exercise in Parkinson's disease. Exercise intensity and duration should be tailored to the individual, but "more is not always better" should not be transformed into "longer or more intensive exercise is biologically inappropriate."

The commentary should acknowledge that:

- exercise responses are heterogeneous;
- interval and continuous training can both be beneficial;
- progressive overload is a central principle of physical adaptation;
- fatigue may require adjustment rather than abandonment of conventional exercise;
- mitochondrial adaptations commonly arise through repeated physiological stress followed by recovery.

The proposed micro-session model should be positioned as a complementary option that requires comparison with existing programmes, not as a replacement justified by an already established mechanism.

10. The disease-modification claim should be removed or very substantially moderated.

The most concerning claim is that repeated short sessions may support the maintenance of remaining dopaminergic neurons and potentially slow disease progression. The manuscript provides no clinical evidence that the proposed intervention is neuroprotective or disease-modifying.

Even as a hypothesis, this claim requires a much more rigorous mechanistic foundation and careful wording. Improvements in symptoms, function, fatigue, or exercise tolerance must not be equated with reduced neurodegeneration.

I recommend removing statements suggesting that this protocol may slow the trajectory of Parkinson's disease from the abstract and conclusion. At most, the author could state

"Whether repeated interval-based exercise influences biomarkers related to mitochondrial function or neurodegeneration would require dedicated mechanistic and longitudinal investigation."

Until such evidence exists, the commentary should focus on symptom modulation, feasibility, and short-term motor performance.

11. The proposed effects of meditation on ATP availability are highly speculative.

The manuscript proposes that meditation may reduce competing cognitive and emotional processing and thereby preserve ATP for motor function. Although meditation may benefit anxiety, mood, stress, and quality of life, the inference that it reallocates ATP to motor circuits and improves gait, freezing, postural stability, or tremor has not been demonstrated.

The manuscript acknowledges some of this uncertainty, but elsewhere the explanation becomes more assertive. Claims that meditation could reduce tremor by decreasing signals competing for priority in the basal ganglia are particularly speculative and should either be removed or explicitly presented as untested predictions.

A more defensible position would be that meditation may reduce stress or anxiety, which can exacerbate symptoms in some individuals, while any direct energetic mechanism remains unknown.

12. The subtype-specific predictions are unsupported.

The manuscript suggests that people with akinetic-rigid symptoms may benefit particularly from rhythmic intervals, that tremor-dominant patients may respond better to meditation, and that those with postural instability and gait difficulty may benefit from the interval structure.

These subgroup predictions are not supported by the cited evidence. They give the proposed model an appearance of clinical precision that it does not yet possess. Unless the author can provide a stronger mechanistic and empirical foundation, these statements should be removed or clearly identified as highly tentative research questions.

13. Alternative explanations should be discussed more fully.

A strong hypothesis commentary should not only present a novel model but also identify observations that could distinguish it from competing explanations.

The author should discuss how the energetic-dynamics hypothesis differs empirically from explanations based on:

- dopaminergic fluctuations;
- attentional compensation;
- external cueing;
- anxiety and stress;

- central fatigue;
- motor automaticity;
- executive dysfunction;
- placebo or expectancy;
- cardiovascular and autonomic responses;
- peripheral muscular fatigue;
- practice and familiarisation.

The manuscript would benefit from explicit falsifiable predictions. For example:

- Do motor improvements correlate with central or peripheral bioenergetic biomarkers?
- Do they occur after rhythmic interval exercise but not after energy-matched continuous exercise?
- Does the duration of recovery correlate with the proposed ATP response?
- Are changes independent of cueing and expectancy?
- Do responses differ according to medication state?
- Can the proposed central mechanism be distinguished from changes in skeletal-muscle metabolism?

This would turn an interesting narrative into a more rigorous scientific framework.

14. The proposed pilot-study design is not sufficient to test the mechanism.

The suggested pilot study could evaluate feasibility and preliminary clinical effects, but it would not directly test the energetic mechanism. Demonstrating improvement after short rhythmic sessions would not show that ATP availability caused the improvement.

A more informative study would include at least one comparator, such as:

- time- and intensity-matched continuous exercise;
- non-rhythmic interval exercise;
- rhythmic cueing without exercise;
- seated exercise with different work-to-rest ratios;
- an attention-control condition.

Outcomes should include blinded objective motor assessments where feasible, not only self-reported energy and checklists. Medication timing, circadian variation, learning effects, and spontaneous symptom fluctuation should be standardised or modelled.

If the proposed mechanism is central, the study should also include a feasible mechanistic measure. The author should acknowledge that peripheral blood or skeletal-muscle markers would not necessarily reflect ATP availability within basal ganglia networks.

15. The literature base is too limited for the breadth of the claims.

The commentary cites only 13 references despite making broad claims across mitochondrial biology, Parkinson's pathophysiology, basal ganglia neurophysiology, exercise science, dance therapy, meditation, neuroplasticity, rehabilitation, and clinical subtypes.

A commentary need not be a systematic review, but its central assertions should be supported by a sufficiently representative literature base. The author should expand and balance the references, particularly regarding:

- mechanisms of motor fluctuations and freezing;
- exercise-induced neuroplasticity in Parkinson's disease;
- aerobic and interval training;
- mitochondrial responses to exercise in neurological populations;
- neural mechanisms of rhythmic auditory stimulation;
- dance interventions beyond tango;
- fatigue and exercise intolerance;
- motor learning in Parkinson's disease;
- evidence concerning exercise and disease progression.

The manuscript should also avoid relying on a single reference to support multiple broad physiological assertions that the cited source may not directly address.

Minor comments

1. The title should signal that this is a hypothesis or conceptual framework. For example: **An Energetic-Dynamics Hypothesis for Structuring Exercise in Parkinson's Disease**

This would more accurately represent the evidential status of the proposal.

2. The abstract should use terms such as "proposes," "hypothesises," and "may contribute" consistently. Statements that the framework "clarifies" or "explains" clinical phenomena should be

moderated.

3. “Parkinson’s disease” is generally preferable to “Parkinson’s” when referring to the condition in formal scientific writing.
4. The claim that tango “stands out as unusually effective” should be qualified according to the certainty and heterogeneity of the comparative evidence.
5. “Mitochondrial activation” should be defined. Acute changes in metabolic flux, mitochondrial respiration, enzyme activity, and long-term mitochondrial biogenesis are not interchangeable.
6. Biogenesis, mitophagy, enzyme adaptation, and changes in membrane potential occur on different timescales. They should not all be presented as immediate responses to an ATP “dip” during a single contraction.
7. The term “energetic collapse” is dramatic and undefined. A measurable physiological construct should be used instead.
8. “Posture tax” is memorable but informal. It may remain as an explanatory metaphor if clearly identified as such, but it should not replace physiological terminology.
9. The assertion that fine motor activities may require greater basal ganglia ATP demand than gross motor activities is unsupported and should be removed unless evidence is provided.
10. The statement that soundtracks make exercise easier for “almost everyone” is overly broad.
11. The safety of twice-daily unsupervised exercise should not be assumed, particularly in people with advanced disease, cognitive impairment, dyskinesia, autonomic dysfunction, or significant comorbidities.
12. The suggested outcomes should distinguish immediate performance effects from sustained clinical change.
13. Gait speed, stride variability, and freezing frequency require valid and reliable measurement procedures. A home checklist alone would not be sufficient for all outcomes.
14. The manuscript should clearly distinguish fatigue, subjective energy, exercise intolerance, and mitochondrial dysfunction.
15. The conclusion currently repeats the most speculative claims and should instead emphasise that the proposed protocol is low-cost and testable but not yet clinically validated.

Suggested revision of the central conclusion.

The conclusion could be rewritten along the following lines:

This commentary proposes that the timing and recovery structure of exercise may be an underexplored determinant of short-term motor responses in people with Parkinson's disease. Short, rhythmically cued movement intervals separated by brief recovery periods may offer an accessible and adaptable format, particularly for individuals who have difficulty tolerating longer sessions. The hypothesis that such intervals influence motor performance through acute changes in cellular energy availability remains untested and should be distinguished from established effects of rhythmic cueing, practice, attention, and social engagement. Controlled studies comparing different work-to-rest structures and incorporating mechanistic as well as clinical outcomes are required before this approach can be recommended as an evidence-based intervention.

Overall assessment.

This is a creative and potentially stimulating commentary. Its principal strength is that it proposes a simple and falsifiable intervention derived from a broader mechanistic idea. Its major weakness is that the manuscript currently presents a long chain of indirect inferences with a level of certainty not supported by the evidence.

The article could make a useful contribution if it is comprehensively reframed as a hypothesis-generating piece. This would require:

- more precise neurophysiological language;
- a clear distinction between evidence and speculation;
- fuller consideration of alternative mechanisms;
- removal of unsupported disease-modification claims;
- more balanced treatment of established exercise and rehabilitation evidence;
- a substantially expanded literature base;
- a study design capable of testing the proposed mechanism rather than merely demonstrating feasibility.

In its present form, I do not consider the claims sufficiently supported for peer approval. A substantially revised version, explicitly presented as a testable complementary hypothesis rather than an established explanation or clinical prescription, would merit reassessment.

Declarations

Potential competing interests: No potential competing interests to declare.