Qeios

Peer Review

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

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Overall Assessment

The paper proposes an intriguing and original hypothesis suggesting that moment-to-moment fluctuations in motor performance in Parkinson's disease (PD) may be partly explained by unstable mitochondrial ATP availability rather than solely by dopaminergic depletion and basal ganglia dysfunction. Building upon this energetic-dynamics framework, the author argues that the beneficial effects of tango dancing and other rhythmic interventions derive from a favorable pattern of brief activity periods interspersed with short recovery intervals, and proposes a simple home-based exercise strategy based on these principles. The manuscript is clearly written, thought-provoking, and addresses an important unmet need in Parkinson's rehabilitation.

The energetic perspective is intellectually stimulating and may generate useful future research questions. However, many of the central claims extend considerably beyond the evidence currently presented. Several mechanistic interpretations are speculative and are often written in a manner that implies causality despite limited empirical support. In its current form, the manuscript would benefit from a more balanced discussion of competing explanations, a clearer distinction between established evidence and hypothesis, and substantial moderation of conclusions regarding clinical efficacy and disease-modifying potential.

doi.org/10.32388/GWUB3Y

Major Comments

1. The Central Hypothesis Remains Largely Speculative

The manuscript presents the energetic-dynamics model as a plausible explanation for symptom fluctuations in Parkinson's disease. While mitochondrial dysfunction is well recognized as an important contributor to PD pathophysiology, the article frequently moves from established observations to mechanistic assertions without sufficient supporting evidence.

For example, statements suggesting that:

- fluctuations in ATP availability directly explain freezing episodes,
- ATP instability is responsible for variability in DBS responsiveness,
- rhythmic exercise produces rapid improvements primarily through increased ATP availability,

remain hypotheses rather than demonstrated findings.

The manuscript would be substantially strengthened by consistently differentiating between:

- established evidence,
- biologically plausible mechanisms,
- personal theoretical interpretations.

A more cautious wording throughout is recommended.

2. Overemphasis on ATP as the Primary Driver of Motor Variability

Parkinsonian motor fluctuations are multifactorial phenomena involving:

- dopaminergic depletion,
- altered network synchronization,
- maladaptive oscillatory activity,
- sensory integration deficits,
- attentional mechanisms,
- autonomic dysfunction,
- medication pharmacodynamics.

The manuscript occasionally presents energetic failure as a more parsimonious explanation than these established mechanisms.

The discussion should acknowledge that energetic dysfunction may represent one component of a multidimensional process rather than an alternative explanation that supersedes current models.

3. Interpretation of Tango Literature

The section describing tango as a uniquely effective intervention is interesting but somewhat selective. The current text implies that immediate clinical improvements cannot reasonably be explained by neural adaptation and therefore must predominantly reflect transient ATP enhancement.

This conclusion is not sufficiently supported.

Alternative explanations include:

- external cueing,
- attentional engagement,
- sensory-motor synchronization,
- emotional activation,
- enhanced motor planning,
- increased movement confidence,
- social interaction effects.

The author should discuss these mechanisms as potentially complementary rather than mutually exclusive.

4. Claims Regarding Disease Modification Are Premature

Several passages suggest that repeated ATP enhancement may support neuronal maintenance and potentially slow disease progression.

While biologically appealing, there is currently no direct evidence presented that:

- the proposed exercise pattern increases cerebral ATP reserves,
- such changes influence neuronal survival,
- disease progression can be modified through the proposed intervention.

These statements should be reframed as hypotheses to be tested rather than anticipated outcomes.

5. Limited Discussion of Existing Exercise Research

The proposed exercise model focuses heavily on tango-derived interval structures. However, substantial evidence exists supporting benefits from:

- treadmill training,
- cycling,
- resistance training,
- tai chi,
- Nordic walking,
- boxing programs,
- dance interventions other than tango.

The discussion should better integrate this broader rehabilitation literature and explain how the proposed framework relates to existing evidence.

6. Lack of Quantitative Biological Evidence

A major limitation is the absence of direct evidence connecting:

- ATP production,
- mitochondrial function,
- acute motor improvement,

within the context of Parkinson's disease.

Many cited studies document mitochondrial dysfunction or exercise-induced mitochondrial responses in general populations rather than demonstrating the specific mechanisms proposed here.

The manuscript should explicitly acknowledge this gap.

7. Meditation Section Requires Further Justification

The suggestion that meditation may improve motor function by conserving ATP is innovative but highly speculative.

The manuscript currently provides limited mechanistic or experimental support for this proposal.

Consider presenting this section more explicitly as an exploratory future direction rather than an extension of the central model.

Minor Comments

1. Terminology

The term**"energetic dynamics"** is appealing but should be clearly defined early in the manuscript.

A concise operational definition would improve clarity and reproducibility.

2. Biological Precision

Several expressions such as:

- "powering basal ganglia circuits,"
- "ATP voltage,"
- "energetic windows,"

are useful metaphors but may not accurately describe neurophysiological processes.

More precise scientific language would improve the manuscript.

3. Fine Motor Versus Gross Motor Tasks

The proposition that handwriting may impose greater ATP demands than walking is interesting but currently unsupported by direct evidence.

This claim should either be referenced appropriately or described as speculative.

4. Home-Based Protocol

The proposed intervention is practical and patient-centered. However, recommendations regarding:

- 3-minute intervals,
- 1-minute recovery periods,
- twice-daily frequency,

appear largely derived from theoretical reasoning rather than empirical validation.

This limitation should be clearly acknowledged.

5. Figures

The manuscript contains no figures or conceptual diagrams.

A schematic illustration of the proposed energetic-dynamics model would substantially improve readability and conceptual clarity.

Strengths

1. Original and creative hypothesis.
2. Clinically relevant focus on symptom variability.
3. Strong emphasis on translational rehabilitation.
4. Practical and low-cost intervention proposal.
5. Readable and engaging narrative style.
6. Generates clear, testable predictions for future research.

Final Recommendation

This commentary presents an innovative and thought-provoking framework that attempts to integrate mitochondrial dysfunction, exercise physiology, and clinical variability in Parkinson's disease into a unified explanatory model. The article is well-written, accessible to a broad readership, and succeeds in generating novel hypotheses regarding the relationship between energetic capacity and motor performance. Furthermore, the proposed home-based exercise protocol is practical, inexpensive, patient-centered, and addresses an important unmet need in Parkinson's rehabilitation. The manuscript, therefore, has potential value as a hypothesis-generating contribution and may stimulate future experimental and clinical investigations.

Nevertheless, many of the manuscript's central conclusions currently extend beyond the available evidence. Several mechanistic interpretations are presented with a degree of certainty that is not yet justified by existing experimental data, particularly regarding ATP fluctuations as a primary determinant of motor variability, the proposed mechanisms underlying tango's effectiveness, the role of meditation in preserving energetic resources, and the suggestion that the intervention could potentially influence disease progression. The discussion would benefit from a more balanced consideration of established

models of Parkinson's pathophysiology, a clearer distinction between evidence and speculation, and a more explicit acknowledgment of the limitations of the proposed framework.

For these reasons, I recommend **Major Revision**. With substantial revisions focused on strengthening scientific rigor, moderating causal claims, expanding discussion of alternative explanations, and clarifying the speculative nature of the proposed model, this manuscript could become a valuable and stimulating contribution to the ongoing discussion of exercise-based interventions and mechanistic hypotheses in Parkinson's disease.

Declarations

Potential competing interests: No potential competing interests to declare.