Anatomy of an NIH Aims Page

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Consider the aims an executive summary and outline for your entire grant. As a reviewer, I can pretty much understand the whole grant from a good aims page, and establish my initial score, and use the rest of the grant to understand the details. So it is important to make sure it is very clear, succinct, and that the main points are clearly findable.

> *Specific aims guidelines from the NIH sf424*
> State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved.
>
> List succinctly the specific objectives of the research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address

Great aims pages have very particular anatomical elements that help them with this herculean task. But once it is crafted well, the aims page provides a clear structure for the rest of the grant.

Specific anatomical elements are needed to create a complete and convincing roadmap of your study that forms a compelling argument that makes them want to support your grant. Of course anatomy is just the parts of an animal, but they have to work together in a specific way to make it work. Just because I have all the part of the airplane, doesn't mean it will fly. So we need to understand not just the FORM, but also the FUNCTION of the anatomy.

I promote the WHY than WHAT model of writing. Tell me *why* I should care, and then *what* you will do about it. So let's understand what the reviewer is trying to do to motivate how you should write your aims.

The WHY: It is important that the reviewer can easily scan your specific aims and find these elements again and again as they will use this page in several ways. Here is how I use the aims page, and these events typically take place on different days:

- I scan the aims of a pile of grants to **form an initial impression** and figure out the order I'll read them in. At this point I'll know which ones I'm excited about and will be easy to understand versus the one's I'm going to have to make sure ready to
- I'll **read your aims and proposal**–and get interrupted–and scan to the aims to re-orient myself.
- After putting down the grant I'll **compose an initial written review**. I go back to the specific aims page again to find the main points, and consider the messages I would like to convey.
- Then I'll **re-review the proposal** to check certain points and make sure I've done a fair and comprehensive review.

So the main take-away is that most of the time I will not be reading your aims page straight through, but trying to find information that I need for a variety of purposes. The specific aims page prime the reviewer to read the rest of the grant and have any questions that arise answered.

The WHAT: Here are the things I'm looking for, and generally these go from broad to more specific in scope, and in the suggested paragraph. **These elements need to be writing clearing and explicitly in a single sentence.** Try writing them down before you start writing your aims page.

- Compelling and important **gap in scientific understanding being addressed by the proposal**.
- **Impact** and **innovation,** why is it new and important?

- The **scientific or clinical barriers toward a long term goal** that will be addressed
- The **objective** of the proposal – what is the scope of the project and techniques used? Species, type of experiments, types of measures.
- The **expertise of the research team** – why are they the perfect team for the project
- The **hypothesis** or being addressed. This should be general, and not specific to your approach.
- A **rationale for the proposed aims** in plain language; I should get an idea of the experiments
- Any **preliminary data** supporting the proposal
- The **predicted outcomes**, i.e. based on the hypothesis and experiments, what will you find? What are the metrics used?
- The **specific aims**. These are your intellectual deliverables. Make it clear what we will learn from your work.

The easier to it is for the reviewer to find these points and to digest them into an effective review, the happier the reviewer will be about supporting your grant. The more these points form a compelling story about you and your research that leads your reviewer to come up with your experiment before you present them the more enjoyable it will be for the reviewer. Make your reviewer feel smart!

FORM and FUNCTION of a specific aims page: Here is a suggested format or body plan that I try to start with, but each grant then needs to be tailored to its needs. Each paragraph should get more specific

First paragraph: This should introduce the problem the YOU are addressing, and some idea about why or how you are doing that and why it is important. Do NOT tell me some general facts about the disease or problem that you're studying, UNLESS they are ones that you are addressing. For example, do not tell me the economic impact of stroke, unless this is a problem that your proposal addresses, which would be an implementation study. You can save these facts for the significance section, briefly. **Most importantly, get the reviewer excited about your proposal in the first paragraph to set the stage.**

- Long term goals, barriers addressed, and impact should go here.
- In some cases, it may be appropriate to put an overall hypothesis here or introduce your own published data and expertise in this paragraph.

Second paragraph: Your research objective should appear no later than the second paragraph. The reviewer's goal is to find out what you propose so get there as fast as possible. Any background information should be in the context of how it motivates what you will do. **Make sure I would know what the proposed research looks like.** What kind of research techniques and measurements?

- Introducing your research team expertise here may be appropriate
- Preliminary data may be useful here
- Sometime you can put the overall hypothesis here.

Third paragraph: State your hypothesis and use this paragraph to explain your aims in colloquial terms. Let me know how the aims provide an integrated approach to the problem. Why do they go together? What are the different puzzle pieces to our knowledge that each aim uniquely provides. Here it is helpful to refer to **an overall figure of your aims**. What are the predictions that support the impact and innovation?

Specific Aims: There should be no surprises by the time I read the specific aims. I should be able to anticipate what these are by the time I get here. This is your chance to get **more specific**. The written aims should be treated like deliverables. What is the value of the aims, and what will the research community gain? Make sure it isn't just a task or characterization. It could be more like demonstrate that X affects Y. Or identify that mechanism X underlies behavior Y. These are more like titles of a thesis.

De-risking your Aims

A word about how to structure your aims for success…Aims need to be independent, and you need preliminary data for each of them. So how can you really do anything new?

Think about each Aim as a series of papers that address a common goal and build your dependencies within an aim. It helps to explicitly write down the titles of the papers you expect to write. Each aim might work as a thesis for a PhD student. Often the first paper establishes a basic finding, and the next ones are based on it, digging in deeper. That is the second and third paper DEPENDS on the first paper. That is ok, because the overall Aim is still fulfilled even if you don't get to the third paper.

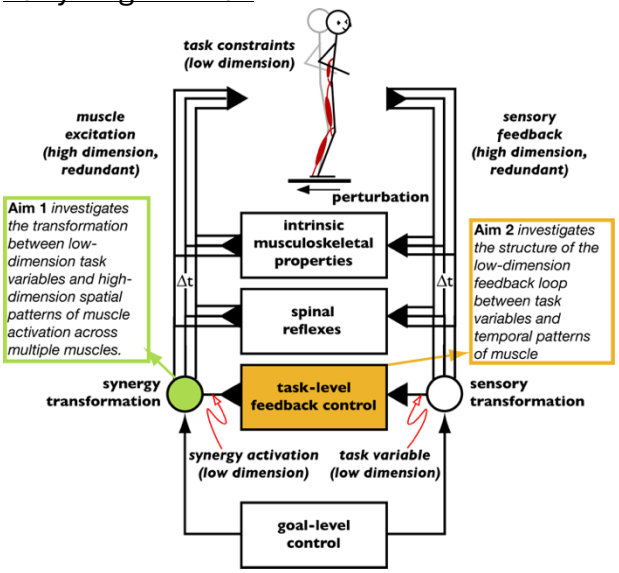
Think about the Aims as fitting together to address your objectives from different approaches. Segregating approaches across aims removed dependencies and makes writing about the aims easier.

Make a figure

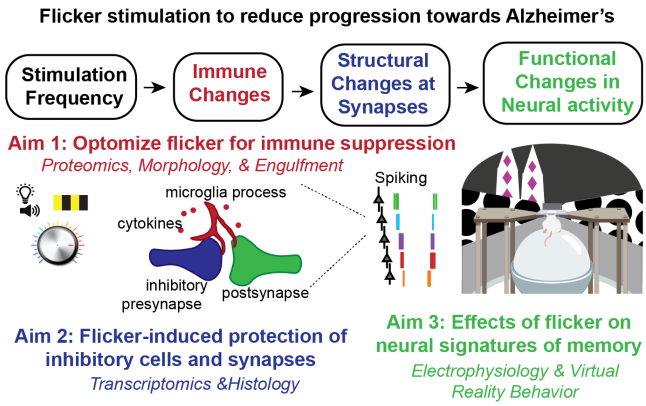
It's important to generate an overall figure to provide a graphical abstract of your aims. A picture is not only worth a thousand words for the reviewer, but it also provides a structure for you to write about and explain. It can show a whole system and the specific aspects you'll study within it. It can show how the different aims probe different parts of the system.

Have a figure and then use your aims page to talk about it. It could go on the specific aims page itself, or put it on the next page, right before the significance section of the research strategy.

Early Ting NIH R01

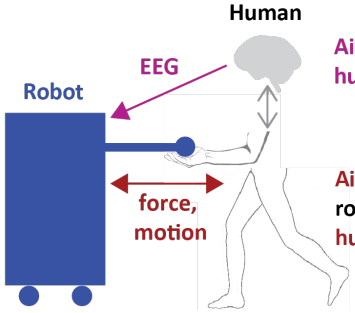


Courtesy Annabelle Singer, NIH R01



Ting/Ueda NSF M3X grant

Aim 1 (Machine): develop and validate a personalized bidirectional pHRI controller to alter gait



Aim 3 (Mind): discern human mental state

Aim 2 (Motor): adapt robot controller to human motor state

Here is an example from an R21 that scored well.

Introduces the problem specific to the proposal

Muscle spindles provide critical sensory information to guide balance and movement, but we still do not understand their firing during functionally-relevant active conditions. Much of what we know about muscle spindles in humans and animals arises from passive conditions, yet efferent commands to gamma motor neurons ("gamma drive") innervating muscle spindles can dramatically shape the sensory signals from muscle spindles based on internal state, i.e. attention, experience, and emotion[1–4]. Muscle spindles are critical to control of locomotion and balance through hierarchical neural circuits across the spinal cord, brainstem, and cortex. The inaccessibility of both efferent gamma signals to and afferent sensory signals from muscle spindles in active conditions creates a critical **scientific barrier** to understanding fundamental principles of sensorimotor control and a **clinical barrier** to treating debilitating symptoms such as spasticity affecting patients with cerebral palsy, stroke, spinal cord injury and other neurological disorders[5].

Impact on important research barriers

Approaches used

We propose a **novel combination** of prediction from a **biophysical model of the muscle spindle** with **direct recordings from human leg muscle spindles** using microneurography and **muscle fascicles** using ultrasound. Recent advances by **PI Ting** and **Co-I Simha** using a multiscale biomechanical muscle spindle model (Fig. 1A) reveal that diverse firing patterns depend critically on length and force of the muscle spindle embedded within the muscles, which differs from externally-measured biomechanical variables[6,7]. Indeed, one of the two studies measuring lower limb muscle spindle firing during voluntary movement suggests a dependence on muscle fascicle velocity, but was carried out in 1978 prior to ultrasound technology to measure muscle fascicle kinematics[8]. More recently, **Collaborator Bent** demonstrated the relationship between muscle spindle firing and muscle fascicle length during lower limb passive movements[9] (Fig. 1F), as well as a burst at stretch onset; both features are predicted by our biophysical model[7] (Fig. 1E). **Collaborator Blouin** used a servomotor to impose sway-like ankle motions and found muscle spindle firing reflected ankle velocity and displacement (Fig. 1G), but reduced fidelity during tonic muscle activity[10], likely due to decoupled joint and muscle motion.

Qualifications of the team and preliminary data

Objective is why and what we will do

Hypothesis is not specific to study

Our **objective** is to identify the role of gamma drive in shaping leg muscle spindles during *voluntary* rhythmic movements and during standing balance control. We **hypothesize** that gamma drive to muscle spindles enables dissociation of *intended versus imposed* muscle state. The scant recordings from gamma motor neurons during cat locomotion suggest that gamma static drive encodes intended muscle state, whereas gamma dynamic drive heightens burst of firing at transitions between posture and movement[11]. Our muscle spindle model takes both gamma static and gamma dynamic drives as input, generating a wide range of possible muscle spindle firing patterns that we will compare to experimental results from **Aim 1 and 2** (Fig. 1A). In **Aim 1** we will use the expertise of **Dr. Bent** to measure muscle spindle activity from awake humans in *voluntary* vs *imposed* sinusoidal ankle movements (Fig. 1B). In **Aim 2** we will use the expertise of **Dr. Blouin** in designing robotic devices that can decouple body part movements during human standing balance to identify sensorimotor control mechanisms and record from human muscle spindles during *natural* and robotically-*assisted postural sway* (Fig. 1C). We will use microneurography to measure spindle activity in plantarflexor muscles that are typically active during standing balance and also have a high density of muscle spindles[12]. We will also measure muscle fascicle kinematics using ultrasound, muscle activity using electromyography (EMG), and joint torque based on load cells and joint kinematics. We **predict** that the relationship of muscle spindle Ia afferent firing will differ qualitatively during voluntary versus imposed conditions, demonstrating a decoupling of muscle spindle firing and objective biomechanical metrics. We further **predict** that the altered relationships between muscle spindle firing and muscle fascicle mechanics can be reproduced *in silico* based on differences in gamma static and gamma dynamic drive.

Explain why we have two aims and how they go together

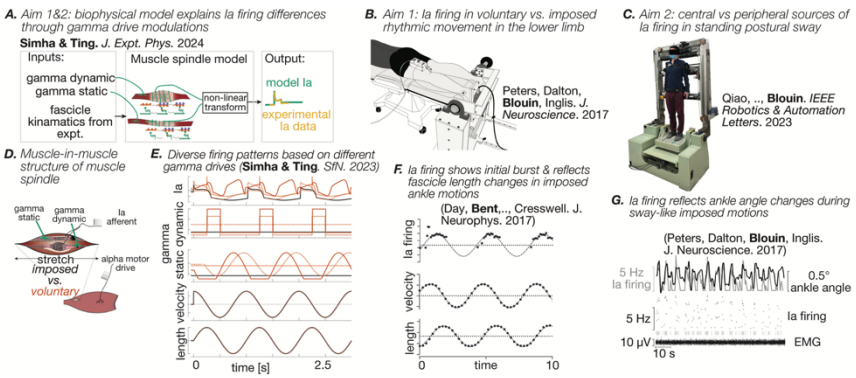
Predictions showing we have testable hypotheses using our approach

Aims are specific in what intellectual knowledge we will come about

Aim 1: Identify differences in muscle spindle Ia afferent firing and gamma drive between voluntary vs. imposed rhythmic movement in the lower limb. First, in the *voluntary* condition, participants will lie prone and move their ankle sinusoidally against a load using eccentric and concentric activation of plantarflexors (Fig. 1B). Next, in the *imposed* condition, ankle angle changes will be driven by the motor to match fascicle length changes from the *voluntary* condition while participants will be instructed to maintain muscle activation similar to the *voluntary* condition using visual feedback. Based on our prior experimental results, we **predict** that recorded muscle spindle firing in the *voluntary* condition will be less coupled to fascicle length than the *imposed* condition and will reflect fascicle velocity. Based on our preliminary modeling results, we **predict** that simulated muscle spindle sensitivity to fascicle velocity will arise from sinusoidal gamma static drive, and sensitivity to movement transitions will arise from higher gamma dynamic drive.

Predictions refer to specific outcome measures

Aim 2: Identify central vs. peripheral sources of muscle spindle Ia afferent firing during standing postural sway. First, in the *natural* sway condition, participants will stand upright in the robot while strapped to a backboard and balance themselves (Fig. 1C). Next, we will use the robot to *assist* postural stability by altering the amount of backward sway when plantarflexors are activated. Based on prior experimental studies, we **predict** that recorded muscle spindle firing will be decoupled from ankle motion, and dependent on muscle fascicle stretch and muscle activity; firing will be reduced when the robot assists postural stability. We **predict** that simulated muscle spindle firing in postural sway will depend on muscle fascicle length (natural sway) or fascicle velocity (assisted sway) and gamma drive reflecting the intent to move the body.



Think like a reviewer. Test yourself on an aims page.

Can you go through and find all of the parts and feel comfortable that all of the key points of the grant are explicit and easily findable, forming a compelling story?

This is an R01 renewal, but you can still refer to your unique expertise in the first paragraph.

This renewal project brings the brain into our neuromechanical understanding of balance control, providing mechanistic insight into relationships between non-motor function, balance control, and falls in Parkinson's disease (PD). In the prior funding period, **MPI Ting** began using electroencephalography (EEG) to identify relationships between cortical activity during balance control and individual differences in perception[1], cognition[2,3], dual-task performance[4], and motor[3–5] function in healthy young adults (YA), older adults (OA), and participants with PD. **MPI Borich** contributed state-of-the art EEG analysis that we now leverage to gain mechanistic insight into the results of the prior funding period by **MPI Ting** with **Co-I's McKay** and **Factor** that revealed associations of impaired perception, cognition, and/or muscle activity to balance impairments and falls in PD[6–10] (Fig. 2). We aim to identify electrophysiological biomarkers and neural mechanisms of motor and non-motor symptoms of PD, addressing **scientific barriers** to advancing treatments that mitigate complex and disabling PD symptoms. If successful, we will advance toward our **long-term goal** of developing mechanistic, personalized treatments to reduce falls in PD that target individual variations in neural circuit dysfunction.

Our **objective** is to identify precise spatiotemporal cortical activity patterns underlying perceptual-motor (**Aim 1**) and cognitive-motor (**Aim 2**) interactions in PD and their relationships to balance control mechanisms (**Aim 3**) (Fig. 1). Analogous to a treadmill stress-test using electrocardiography to assess heart function, we will use a well-controlled *balance probe* to generate an *electrophysiological profile* during behavior that can be directly compared across individuals and trials on millisecond timescales to understand functional impairments. Our prior studies in young adults (YA) and older adults (OA) show that discrete balance perturbations[1,3,9] evoke cortical responses primarily localized to the supplementary motor area (SMA) and associated with perceptual, cognitive, and motor function (Fig. 2). The need to understand SMA dysfunction in PD is being increasingly recognized[11] as it integrates sensory and cognitive inputs, and plays a role in sequential movements[11,12]. Our **preliminary data** show reduced SMA activity in PD participants in balance probes, with highly distributed cortical activity consistent with impairments in perception, cognitive, and motor function.

We **hypothesize** that increased cortical contributions to balance underlie perceptual-motor and cognitive-motor interactions that impair mobility. We will record EEG during a whole-body directional perception paradigm (Fig. 4) where pairs of support-surface perturbations of differing directions create a two-alternative forced choice (2AFC) perceptual discrimination dual-task[1,13,14]. We will test PD participants ON and OFF dopaminergic medication (L-dopa) and collect reference data from OA and YA. In **Aim 1,** we characterize perceptual function in relation to preparatory brain state *before* perturbations and the *evoked* spatiotemporal cortical activity (Fig. 3). In **Aim 2**, we assess cortical response adaptation *across* perturbations in relation to cognitive set-shifting and autonomic activity. In **Aim 3**, we identify cortical contributions to agonist and antagonist muscle activity causing muscle co-contraction in balance recovery. Across **Aims,** outcomes will be related to balance ability (narrowing beam[15]) and clinical balance scores (Mini-BESTest[16]), and exploratory analysis will be performed to identify relationships to fall history, prospective falls, and neuroimaging data.

Aim 1: Identify preparatory and evoked cortical activity underlying perceptual-motor impairments in PD. We **hypothesize** that increased cortical beta oscillations (13-30 Hz) reduce perceptual function that impairs balance. We showed higher whole-body directional perception thresholds (~10-30°) in PD versus OA (~5-20°) and YA (~3-10°) correlated with poor MiniBEST scores in PD but not OA (Fig. 4). Our **preliminary data** in PD show more cortical evoked sources in single and dual-task conditions compared to OA (Fig. 3); and greater pre-perturbation SMA beta power in a single task condition[3] is correlated with MiniBEST scores (Fig. 4). Based on results in YA[1], we **predict** greater pre-perturbation SMA beta power during a perceptual dual task will be correlated with worse perception and balance in PD.

Aim 2: Identify evoked cortical activity patterns underlying impairments in cognitive-motor adaptation in PD. We **hypothesize** that impaired SMA reduces the ability to appropriately adapt cognitive and motor output to predictable contexts, impairing balance. We showed that cognitive set-shifting deficits are associated with falls in OA and PD[7]. Our results in YA show that evoked cortical responses in SMA, i.e., the "balance N1", attenuate within pairs of perturbations with predictable timing and decrease progressively over trials. Based on **preliminary data** in OA and PD, we **predict** poor attenuation of SMA response will be associated with worse set-shifting (TMT: Trailmaking test B-A) and Mini-BEST score (Fig. 5), and anterior cingulate cortex (ACC) responses will be associated with electrodermal activity (Fig. 6).

Aim 3: Identify cortical contributions to balance-correcting muscle activity impairing balance in PD. We **hypothesize** that cortical activity causes inefficient balance-correcting muscle activity that impairs balance. Our sensorimotor feedback model predicts subcortically-mediated muscle activity in YA[17–19], OA, and PD, where destabilizing feedback to antagonist muscles in PD is associated with fall history[9]. Our recent work[20] adds transcortical feedback acting at longer delays. Based on **preliminary data**, we **predict** early increases in cortical beta power after perturbations will drive stabilizing agonist activity for maintaining posture (Fig. 7), while later decreases in beta power facilitating voluntary movement will have opposite effects on antagonist activity in OA and PD (Fig. 8, 9), differentially impairing balance.

Based on **preliminary data,** we **predict** L-dopa will exacerbate perceptual-cognitive-motor impairments in PD (Fig. 10).