Study Protocol and Statistical Analysis Plan

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Vigor and the LDR in Parkinson Disease
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A. Abstract:

Dopamine replacement therapy (DRT) is the standard and very effective symptomatic treatment for early to moderate Parkinson disease (PD). The most important DRT component is the Long Duration Response (LDR), a pharmacodynamic effect that builds up over the course of weeks. DRT actions are poorly understood and the basis of the LDR is unknown. As the LDR wanes in advancing disease, PD patients develop troublesome motor fluctuations and increasing disability. LDR kinetics suggest long-term plastic changes in striatal function. Studies of striatal dopamine actions indicate that striatal dopaminergic neurotransmission regulates "vigor;" modulation of the velocity, amplitude, force, or frequency of movements. Vigor is closely allied with the concept that striatal dopaminergic neurotransmission mediates motivation; assessment of act utility and appropriate scaling of actions to perceived rewards. Recent theoretical and experimental results suggest that tonic striatal dopamine signaling is a key determinant of movement vigor. Convergent clinical pharmacologic and experimental data lead to a strong hypothesis that the LDR results from chronic DRT partially restoring movement vigor. This model of the LDR requires stable "records" of action values. Recent non-human primate work on saccadic eye movement vigor indicates the existence of striatal dopaminergic neurotransmission stably encoding motor behavior values for prolonged periods – a potential mechanism for the LDR. Prior experiments examining vigor in PD did not take the LDR into account, resulting in incomplete examinations of the role of vigor deficits in PD. Our long-term goal is to understand the clinically relevant actions of DRT. The primary objective of our proposal is to test the hypothesis that the LDR results from partial restoration of normal movement vigor-motivation. Our secondary objective is to evaluate a potential mechanism underlying the LDR. The rationale for these experiments is that better understanding of the LDR, a clinically crucial component of DRT action, will lead to improved symptomatic therapy. We will study recently diagnosed PD subjects. All subjects will undergo standard evaluations of clinical, cognitive, and motivational features. Subjects will perform incentive motivation tasks assessing movement vigor – motivation coupling to assess our primary hypothesis. A task assessing saccadic eye movement vigor in response to stable value signals will be employed to evaluate our secondary hypothesis. They will perform all tasks before and after LDR induction in both the "practical off" and post-acute treatment states. Validation of our hypotheses would have considerable impact by identifying the functional process underlying the LDR and providing information for uncovering the mechanisms of the LDR. This would facilitate research into LDR mechanisms, provide a rational basis for developing valid animal models of the LDR, and open a new path towards improved symptomatic management of PD.

B. Specific Aims

Dopamine replacement therapy (DRT) is the standard symptomatic treatment for early to moderate Parkinson disease (PD). In early to moderate PD, the most important DRT component is the Long Duration Response (LDR), a pharmacodynamic effect that builds up over the course of days-weeks and can be induced by dopamine agonists. Despite its effectiveness, DRT actions are poorly understood and the basis of the LDR is unknown. As the LDR wanes in advancing disease, PD patients develop troublesome motor fluctuations and increasing disability. Improved understanding of the LDR has the potential to prolong the duration of its effects and could have a significant positive effect on clinical practice.

The kinetics of the LDR suggest long-term plastic changes in striatal function. Recent studies of striatal dopamine actions in PD subjects and experimental animals indicate that striatal dopaminergic neurotransmission regulates "vigor," the force, velocity, or amplitude of actions. Vigor is closely allied to the concept that striatal dopaminergic neurotransmission mediates motivation, which involves the assessment of act utility and the appropriate scaling of actions to perceived rewards. Recent theoretical and experimental results suggest that tonic striatal dopamine signaling, mimicked by dopamine agonist administration, is a key determinant of movement vigor. Convergent clinical pharmacologic and experimental data lead to a strong hypothesis that the LDR results from chronic DRT partially restoring motivational coupling of effort to perceived reward and movement vigor. Prior experiments examining vigor in PD subjects did not take the LDR into account, resulting in incomplete examinations of the role of vigor deficits in PD.

Recent non-human primate work on the control and vigor of saccadic eye movements indicates the existence of basal ganglia circuit changes that stably encode motor action values for prolonged periods. Striatal dopaminergic neurotransmission is critical for establishing this remarkably stable form of value-action coupling. This phenomenon is a plausible circuit level mechanism underlying the LDR.

Our long-term goal is to understand the clinically relevant actions of DRT. The primary objective of our proposal is to test the hypothesis that the LDR results from partial restoration of normal action vigor by reinstating the link between motivation and effort. Our secondary objective is to explore potential mechanisms underlying the LDR. The rationale for these experiments is that better understanding of the LDR, a clinically crucial component of DRT action, will lead to improved symptomatic therapy.

We will study recently diagnosed PD subjects. All subjects will undergo standard evaluations of clinical, cognitive, and motivational features. Subjects will perform incentive motivation tasks assessing movement vigor in response to monetary incentives. Two complementary tasks, one based on modulation of movement velocity and one based on modulation of grip strength, will be employed. To assess whether the recently described stable action-value coupling for saccades is relevant to the LDR, subjects will perform a task that measures saccadic eye movement vigor in response to stable value signals learned prior to LDR induction. Subjects will perform all tasks before and after LDR induction in both the "practical off" and post-acute treatment states.

Specific Aim 1: To use incentive motivation tasks to evaluate the coupling between motivation and movement vigor in recently treated PD subjects before and after LDR induction.
Hypothesis 1A: LDR induction will result in partial restoration of movement vigor in response to monetary incentives in PD subjects in the "practical off" state.
Hypothesis 1B: The magnitude of partially restored movement vigor in response to monetary incentives will correlate with reduced bradykinesia in PD subjects in the "practical off" state.
Hypothesis 1C: Identical effects will be found with an incentive motivation task based on movement amplitude and one based on grip strength.
Specific Aim 2: To use a saccadic eye movement task to assess saccadic eye movement vigor in response to stable value signals in recently treated PD subjects before and after LDR induction.
Hypothesis 2: LDR induction will result in partial restoration of saccadic eye movement vigor in response to previously learned stable value signals in PD subjects in the "practical off" state.

Validation of our hypotheses would have considerable **impact** by identifying a specific functional process underlying the LDR and a potential mechanism of the LDR. This will facilitate research into LDR mechanisms, provide a rational basis for developing valid animal models of the LDR, and open a new path towards improved symptomatic management of PD.

C. Research Strategy

The Long Duration Response in Parkinson disease: Parkinson disease (PD) is the second most common neurodegenerative disorder, affecting approximately 1 million Americans. PD is defined by a constellation of motor features – bradykinesia, rigidity, resting tremor, and postural instability. Bradykinesia, which includes slowed movements and progressive decrements of movement speed and amplitude with movement repetition, is regarded as the core deficit of PD.[1] Motor dysfunction in PD results from reduced striatal dopamine (DA) signaling accompanying degeneration of the DAergic nigrostriatal projection.

DA replacement therapy (DRT) is the cornerstone of PD treatment and is generally very effective in mild to moderate PD. The most effective and commonly used treatment is the DA precursor L-dopa. Synthetic DA agonists, with longer half-lives, are used for monotherapy and as adjunctive agents. These are primarily D2 receptor selective agents, are less potent, and exhibit significantly higher rates of serious side effects. There are 2 major components of patient response to L-dopa treatment – the Short Duration Response (SDR) and the Long Duration Response (LDR).[2-4] L-dopa has a half-life of approximately 1 hour in blood. With typical oral administration schedules (3-4x/day), plasma L-dopa levels are very low at the end of dose intervals. The SDR begins quickly, lasts minutes to hours, and then declines, with clinical effects approximately paralleling plasma L-dopa levels. The LDR is sustained improvement following chronic

treatment which builds up over days to weeks and declines over similar intervals with treatment suspension. The LDR is the major component of treatment response in early PD and is responsible for the fact that many early phase PD patients experience little or no decrement in performance if they miss L-dopa doses. Pharmacodynamic modeling studies suggest that the half-life of the LDR is approximately 8 days, with plausible suggestions of longer half- lives.[5,6]

The LDR wanes with disease progression with increasing importance of the SDR.[7,8] This results in motor fluctuations, including wearing off of drug effect and dyskinesias. Patients require increasing L-dopa doses, frequent regimen adjustments, and adjunctive agents. There is significantly increased incidence of troublesome medication side-effects. Many need Deep Brain Stimulation (DBS) surgery to obtain adequate quality of life.

Initial hypotheses about LDR mechanisms suggested that its existence reflected a brain "buffer" compartment taking up and storing L-dopa and/or DA for subsequent release. This hypothesis was falsified by several experiments demonstrating that DA agonists can initiate and sustain the LDR.[5,9-11] In addition, LDR kinetics are identical in patients with Dopa Responsive Dystonia, a rare disorder of deficient DA synthesis highly responsive to L-dopa treatment.[12] These individuals have normal nigrostriatal terminals and normal DA storage capacity.

<u>The mechanism(s) underlying the LDR are unknown as there have been no subsequent studies investigating the underpinnings of the LDR.</u>

Phasic Dopamine Signaling Does Not Explain the LDR: Striatal DA actions have been the focus of intense study over the past generation. Striatal DAergic neurotransmission is described as mediating a number of important processes, including reinforcement learning, habit formation, action selection, action vigor, and motivation (for discussion of vigor and motivation, see **Approach** below). The best characterized aspect of striatal DA signaling is its role in reinforcement learning. Considerable evidence indicates that rapid (100-300 msec), phasic bursting of nigrostriatal neurons, resulting in discrete boluses of striatal DA, provides a Reward Prediction Error signal for reinforcement learning.[13-15] Observed originally in seminal non-human primate experiments by Wolfram Schultz, studies of this aspect of striatal DAergic signaling dominate the literature on striatal DA actions.

As pointed out by Schultz and others, restoration of phasic nigrostriatal DA signaling is unlikely to occur with L-dopa treatment and cannot account for the effects of L-dopa treatment in PD.[2,16,17] At onset of symptomatic PD, patients have already experienced massive, >60% loss, of motor striatum nigrostriatal terminals.[18] Accompanying nigrostriatal terminal degeneration is loss of dopamine transporters (DAT) located uniquely on DAergic terminals. DAT activity is the primary mechanism for clearing DA from the synaptic cleft. Massive nigrostriatal terminal loss results in both diminished DA release and increased DA extracellular residence time, degrading phasic DA signaling.[19,20] <u>Other components of striatal DA signaling must account for the effectiveness of L-dopa in PD.</u> Schultz suggested that some form(s) of tonic striatal DA signaling accounts for L-dopa effectiveness.[16] LDR kinetics suggests long-term plastic changes in striatal DA actions.

Approach Overview: Our primary objective is to test the hypothesis that the LDR results from partial restoration of a critical aspect of striatal DA signaling: mediation of vigor and motivation (**Specific Aim 1**). Confirmation of our hypothesis would connect the LDR to a fundamental feature of striatal DA action. The burgeoning preclinical and human experimental literature in this area would provide a solid foundation for mechanistic studies of the LDR. Our secondary objective is to evaluate a potential LDR circuit level mechanism (**Specific Aim 2**).

The proposed work is based on collaboration between investigators with strongly complementary expertise. Dr. Albin is a Movement Disorder neurologist and experienced PD clinical researcher. Dr. Lee is a Cognitive Neuroscientist focused on the interactions between cognitive control, motivation, and action. We engaged expert collaborative consultants for critical aspects of the proposed experiments. Dr. Joshua Dudman (HHMI- Janelia Farms) is a leading expert on striatal dopamine signaling and vigor modulation. Dr. Dudman developed the movement amplitude task deployed for **SA1**, a human adaptation of the task his lab

used in influential murine experiments demonstrating DAergic modulation of movement vigor. Dr. Brian Anderson (Texas A&M) is an expert on the task deployed for **SA2**. Drs. Dudman and Anderson agreed to advise us on implementation of these tasks and data interpretation (see attached LOS).

Specific Aim 1: To use incentive motivation tasks to evaluate the coupling between motivation and movement vigor in recently treated PD subjects before and after LDR induction.
Hypothesis 1A: LDR induction will result in partial restoration of movement vigor in response to monetary incentives in PD subjects in the "practical off" state.
Hypothesis 1B: The magnitude of partially restored movement vigor in response to monetary incentives will correlate with reduced bradykinesia in PD subjects in the "practical off" state.
Hypothesis 1C: Identical effects will be found with an incentive motivation task based on movement amplitude and one based on grip strength.

Rationale: A substantial body of data indicates that striatal DAergic neurotransmission mediates vigor – the speed, amplitude, force, or frequency of actions.[21-25] These different aspects of vigor have in common modultion of effort, ultimately the degree of energy expenditure required to accomplish actions. Vigor modulation is closely linked to the motivational role of striatal DAergic neurotransmission. Salamone and others argue persuasively that striatal DAergic neurotransmission is critical for efficient effort allocation by proportioning actions to perceived rewards – the fundamental process of motivation.[21-23] Several studies implicate aberrant movement vigor modulation as the underlying mechanism of PD bradykinesia. An influential experiment by Mazzoni et al. indicates that PD subjects exhibit aberrant estimation of effort-reward tradeoffs of movements.[26] These results were replicated by several groups using a variety of paradigms to assess movement vigor in PD subjects.[27-29] These paradigms generally isolate modulation of movement velocity, force (e.g., grip strength), or amplitude as outcome measures. These outcome variables all reflect effort and in most paradigms, the chosen outcome variable (e.g., amplitude of reaching) is co-linear with other potential outcome variables (e.g., force of reaching).

Consistent with Schultz's suggestion that some form of tonic striatal DA action is critical for treatment of PD, LDR induction by dopamine agonists suggests tonic striatal DA signaling in the LDR. Theoretical and recent experimental evidence indicates that tonic striatal DA signaling is an important mediator of vigor. Niv et al. elaborated a model of reinforcement learning in which subjects make choices about action selection and vigor with the goal of maximizing the net value of rewards per unit time.[30] Faster or more intense movements are more costly.[30,31] Optimal performance requires an effort-reward (cost-benefit) analysis including the costs of action vigor. Simulations with this model recapitulate results of typical animal experiments examining response vigor. In this model, a mechanism is needed to provide a long-term account of the prior average rate of rewards. Niv et al. predicted that tonic striatal dopamine signaling provides the necessary history of prior rate of reward. Zhuang and colleagues tested this hypothesis with partial DAT knockdown (pDATKD) mice.[32,33] These mice manifest chronic, moderate elevation of striatal DA but exhibit normal nigrostriatal neuron phasic activity and normal reinforcement learning. pDATKD mice work more vigorously than control mice for equivalent rewards, exhibiting distorted effort-reward coupling. Panigraphi et al. examined forelimb movement vigor in MitoPark mice, a model of adult-onset, selective nigrostriatal neuron degeneration with slowly progressive bradykinesia.[34] In clever experiments, they demonstrated normal reward contingency learning but impaired ability to scale forelimb movements appropriately. Panigraphi et al. also demonstrated significant improvements in MitoPark mice movement vigor with L-dopa treatment. Remarkably, improved movement vigor did not occur with acute treatment, but only with weeks of daily treatment, a possible LDR analogue.

Converging theoretical work, preclinical experiments, and clinical experiments suggest that DRT improves bradykinesia via partial restoration of normal striatal vigor modulation and that the LDR is the manifestation of improved vigor modulation via partially restored tonic dopamine signaling. There is, however, a critical gap in the chain of data. None of the human experiments adequately controlled for DRT treatment effects. The Mazzoni et al. study was performed in chronically treated PD subjects.[26] Several other experiments evaluated PD subjects during DRT and after withholding DRT for 10-12 hours (the "practical off" state) and obtained analogous results.[28,29] These experiments report reduced vigor modulation in the "practical off" state. The PD subjects in these studies were inevitably beneficiaries of the LDR, confounding comparison of

performance of PD subjects evaluated in the "practical off" state with control subject performances. Rigorous evaluation of the concept that PD bradykinesia results from aberrant modulation of vigor requires human experiments that control for LDR effects. A well designed experiment will assess whether the LDR is correlated with improved vigor, as predicted by our hypothesis.

Procedures:

a) We will study newly diagnosed PD subjects recruited from the Movement Disorders clinics at the University of Michigan. We see approximately 1300 PD patients annually. Subjects must meet Movement Disorder Society (MDS) criteria for PD.[1] Only H&Y1-2 subjects will be enrolled. Exclusion criteria include significant cognitive impairment (Montreal Cognitive Assessment score <24), significant depression (Geriatric Depression Scale [GDS] >5), stimulant use, dopamine agonist treatment, or confounding other neurologic or medical disorders. Subjects will be characterized at each testing condition with standard scales: Parkinsonism – MDS- Unified Parkinson Disease Rating Scale (UPDRS); Mood – GDS; Apathy – Lille Apathy Rating Scale; Cognition – a short battery of selected domain specific tests used previously.[35] Bradykinesia will be quantified with a tapping task used extensively by Nutt et al. in prior LDR studies (see section **c** below).[7,8]

b) Subjects will be studied at pre-treatment baseline and 2-3 months after L-dopa treatment initiation and regimen stabilization. We will only enroll drug-naïve subjects about to start treatment with L-dopa. Subjects will be studied in OFF and ON acute treatment states at baseline and after LDR induction. There will be 4 measurement states: at baseline prior to chronic treatment initiation (OFF-No LDR); at baseline after a standard, acute oral dose (25/250 carbidopa/L-dopa) of L-dopa (ON-No LDR), 2 months after initiation of chronic, stable L-dopa treatment but with no L-dopa for 10-12 hours prior to evaluation (Practical OFF–LDR), and after subjects' usual L-dopa dose (ON-LDR) (**Table 1**).

Table 1:

OFF-No LDR	**Baseline - Treatment Naïve Subject**
ON-No LDR	**Baseline - Treatment Naïve Subject After Acute L-Dopa**
OFF-LDR	**Chronically Treated – "Practical Off" State**
ON-LDR	**Chronically Treated – After Usual L-Dopa**

Practical ON and OFF state measurements will be counterbalanced across individuals. We will recruit both male and female PD subjects, though we expect more male subjects as PD is more common in men. This is a within subjects design and randomization per se is not used. Blinding of study conditions is not feasible. It would be potentially interesting to include a placebo LDR induction arm, but denying PD subjects effective treatment is not ethical. Data analysis will be blinded. It would also be interesting to include a normal subject arm, but this is ethically problematic as it would involve chronic L-dopa treatment. If, however, we obtain results confirming our hypotheses, we will explore inclusion of normal controls in the next phase of experiments.

c) LDR magnitude will be measured by reduction of bradykinesia between the initial OFF-No LDR state and the Practical OFF-LDR state. Comparisons of the On-No LDR state and OFF-No LDR state, and the Practical OFF-LDR and ON-LDR states will measure the SDR. As a measure of bradykinesia, we will use the well-validated tapping task used by Nutt et al. in their experiments defining LDR kinetics.[7,8] With the hand most affected by PD, subjects are instructed to alternately tap 2 manual counters spaced 20 cm apart as rapidly as possible for 1 minute. Subjects will practice several times until they feel comfortable with the task. They will perform 5 trials spaced ~3-4 minutes apart with the initial trial discarded to reduce variation secondary to anxiety. Results of the remaining 4 trials will be averaged to generate a tapping speed (taps/min) for each subject in each condition. This is very similar to the approach used by Nutt et al. (JG Nutt, personal communication).

d) Vigor modulation will be evaluated with two separate incentive motivation tasks; one based on modulation of movement amplitude and one based on modulation of grip strength. The latter is similar to a task used previously in PD subjects by Schmidt et al.[36] It is implemented in the Lee laboratory. This task was chosen because it is relatively easy to use and implement, is compatible with functional neuroimaging, and results in PD subjects were replicated using a very similar task by Chong et al.[28] Briefly, subjects will be tasked with modulating their grip strength in response to monetary incentives. With the hand most affected by PD

symptoms, they will be asked to squeeze a hand dynamometer at the outset of the experiment to measure the strength of their maximum voluntary contraction (MVC). All grip strength targets will be scaled to this value. Subsequently, subjects will undergo a series of trials in which they will be presented with an incentive cue that indicates the level of reward for that trial. They will be informed that on each of these trials they will earn a percentage of the incentive shown that is directly proportional to how hard they squeeze on that trial. While healthy individuals generally increase grip strength with increasing incentive values on this task, previous work has shown that PD patients are impaired in their ability to modulate their grip strength in this way. To ensure that any deficits found are due to motivational vigor and not simply a reflection of impaired muscle power, we will incorporate control trials in which PD subjects are instructed to increase grip strength to similar target levels of force without monetary incentives.

We will use a variant of the mouse task used in Panigrahi et al.[34] This task was inspired by tasks used in human PD studies.[26,27] A spring loaded joystick that returns to a center position if no force is applied is used. Application of force to the joystick displaces it from the center and is monitored to detect the real-time trajectory of the movement. A water reward is delivered 1 second after the joystick passes a specified amplitude threshold. For human equivalent tasks, a flexible range of manipulanda (varying the force requirements) and flexible visuomotor feedback during training and/or testing are deployed. Varying force requirements for reward measure reward-effort coupling. Use of 2 incentive motivation tasks is complementary and provides a more stringent test of our hypothesis. As these tasks are different measures of movement vigor modulation, we should obtain similar and strongly correlated results. Confirmation of our hypothesis with the amplitude modulation task will provide reassurance that we are studying the same vigor modulation phenomenon studied in basic investigations. The grip strength modulation task is better suited to functional imaging experiments and will be a valuable platform for future experiments.

e) Analysis Plan: Hypothesis 1A; Our primary comparisons will be performance on the incentive motivation tasks before and after LDR induction. We predict that improved performance on the incentive motivation tasks will be apparent between the OFF-No LDR and Practical OFF-LDR conditions but not in comparisons between the other conditions. Data will be analyzed via 2-Way Repeated Measures ANOVA followed by post-hoc tests with incentive level and treatment condition as the factors and multiple comparison adjustments. Based on the Schmidt et al. data[36], we estimate that achieving power of 0.9 at an effect size of $\eta^2 = 0.15$ requires complete data from 16 subjects. Based on experience with complex, serial imaging studies, we project a 10% dropout rate (~2 subjects). To compensate for dropouts, we will recruit 20 subjects. Hypothesis 1B; We will correlate changes in performance on the incentive motivation task with the change in tapping rates with Pearson or Spearman correlation tests. Hypothesis 1C: We will correlate the results of the amplitude modulation based and grip strength based incentive motivation tasks with Pearson or Spearman correlation tests.

Interpretations and Potential Problems: If our predictions are correct, we will validate the connection between the LDR and partial restoration of vigor modulation. Falsifying this hypothesis will be equally valuable as it would direct research on the LDR towards different features of striatal DA action. We may, for example, find a relationship between the SDR and improved vigor modulation, which would direct research towards the mechanisms of the SDR. As discussed above, prior experiments evaluating vigor modulation in PD have not taken the LDR into account. We may find no clear relationship between vigor modulation and bradykinesia. This would be important as it would cast doubt on the widely accepted concept that PD bradykinesia is the consequence of altered vigor modulation, and potentially re-direct research in this field.

Subject recruitment is a potential obstacle to study completion. Our clinics follow ~1300 PD subjects with ~200 new PD patient visits per year. Our group successfully recruited for trials requiring untreated PD patients such as STEADY-PD and SURE-PD. Our group expanded this past summer with the addition of 2 faculty Movement Disorder specialists primarily committed to clinical practice. Treatment with dopamine agonists is an exclusion criterion and will not affect recruitment. Our Movement Disorders group is conservative in terms of treatment recommendations and the overwhelming majority of our patients initiate therapy with L-dopa monotherapy. If recruitment lags, we will recruit through the Michigan Parkinson Foundation, the major lay PD organization in Michigan with 71 affiliated support groups and a mailing-email list of ~15,000 (see attached LOS). These experiments are straightforward, using simple behavioral tasks. A potential problem is that some patients experience nausea with initial L-dopa treatment, which could

complicate the ON-No LDR assessment. We will reduce the possibility of nausea by 48 hour pretreatment with the peripheral decarboxylase inhibitor carbidopa. Another potential problem is enrollment of subjects with one of the PD mimics (Multiple System Atrophy, etc.). An advantage of our design is that we will be evaluating subjects after treatment initiation, allowing us to gauge treatment responses. Subjects not improving with L-dopa treatment, defined by the MDS criteria of $\geq$ 30% improvement in MDS-UPDRS$_{III}$ score, will be excluded.

Specific Aim 2: To use a saccadic eye movement task to assess saccadic eye movement vigor in response to stable value signals in recently treated PD subjects before and after LDR induction.
Hypothesis 2: LDR induction will result in partial restoration of saccadic eye movement vigor in response to previously learned stable value signals in PD subjects in the "practical off" state.

Rationale: The long half-life of the LDR indicates that it is based on long-term DA mediated striatal plasticity. The computational model of Niv et al. suggests that accurate vigor modulation requires a striatal DA signaling "recording" the long-term prior average value of rewards. Rodent and non-human primate lesion experiments suggest that the striatum mediates estimates of prior reward histories.[37,38] Studying saccadic eye movements in non-human primates, Hikosaka and colleagues described a basal ganglia mechanism stably encoding values of visual stimuli to modulate the vigor of saccadic eye movements.[39,40] Hikosaka et al. presented animals with a large set of fractal images, training them to associate a subset with rewards. Weeks to months later and in unrewarded conditions, animals are exposed to groups of fractal images containing some images associated previously with rewards. Saccadic eye movement vigor was measured. Images associated previously with rewards evoked greater saccadic vigor. In detailed physiologic experiments, Hikosaka et al. established that activity of DAergic nigrostriatal neurons projecting to the caudate nucleus tail are critical for this phenomenon. This demonstration of long-term stable action-value association has features required of a DAergic mechanism "recording" reward history and underpinning vigor modulation.

If this phenomenon underpins vigor modulation, then DRT partial restoration of DAergic signaling in this circuit is a plausible substrate for the LDR. LDR induction is predicted to improve saccadic eye movement vigor in tasks analogous to that used by Hikosaka et al.

Procedures: Subject recruitment, characterization, and test conditions are as described in **Specific Aim 1**.

It is not feasible to train PD subjects on hundreds of fractal images. We will use an analogous task validated well in humans; value driven attentional oculomotor capture (VDAOC).[41-43] A probabilistic learning task is used to train subjects to associate a salient visual stimulus (color) with reward. In a test phase, the previously rewarded stimulus is presented in task-irrelevant context as a distractor. Saccades to the test phase target and distractor are assessed, including percentage of saccades to distractor or target, saccade latency, and saccade duration. Previously rewarded distractor stimuli capture initial saccades and the magnitude of VDAOC is assessed. This task is accompanied by striatal dopamine release.[44] Subjects are trained in a single session and attentional capture is remarkably durable; it persists in test phase experiments months after a single training session.[45] To duplicate the approach used by Hikosaka et al., PD subjects will be trained on reward-color association prior to initiation of L-dopa therapy. VDAOC will be measured in 4 measurement states described above (**Table 1**). Saccades will be evaluated with an Eyelink tracker with a sampling rate of 250 Hz. If we again assume a modest effect size of $\eta^2 = 0.15$, 16 subjects will be sufficient to achieve a power of 0.9. To guard against dropouts, we will target enrolling 20 subjects. Data analysis approach will be similar to that proposed for **Specific Aim 1**.

Interpretations and Potential Problems: Straightforward interpretation of this experiment presupposes validation of our hypothesis that LDR induction is associated with improved modulation of vigor as tested in **Specific Aim** 1 experiments. Assuming validation of our primary hypothesis, we predict that LDR induction will be associated with improved saccadic eye movement vigor (VDOAC magnitude). The analysis approach will be similar to that used for **Specific Aim 1** experiments. The primary comparison will be between saccadic vigor in OFF-No LDR and Practical OFF-LDR conditions. If LDR induction is associated with improved saccadic vigor in the context of successful **Specific Aim 1** experiments, we will have evidence supporting the hypothesis that the stable striatal DAergic signaling described by Hikosaka's group underpins the LDR. This would be an excellent point of departure for future experiments on LDR mechanisms. This experiment will have value even if we falsify **Hypothesis 1**. Regardless of the outcome of the **SA1**

experiments, success with this experiment would support the existence in humans of the interesting and potentially important phenomenon described by Hikosaka et al. in monkeys. It's possible that we might validate **Hypothesis 1** but falsify **Hypothesis 2**. That result would certainly point away from the mechanism described by Hikosaka et al. as underlying the LDR. An alternative interpretation then would be that the dopamine deficient (PD) state impairs value encoding. This could be evaluated in subsequent experiments in which different colors are associated with reward in different training sessions during each of our measurement conditions.

Potential obstacles and responses to problems associated with this experiment are those outlined above for **Specific Aim 1** experiments. This task has not been used in a patient population and a more prolonged training phase may be needed. Initial experiments will assess this potential issue.

D. Recruitment and Retention:

Subjects will include 30-40 with Parkinson disease (PD). For experiments for **SA1** and **SA2**, our power estimates indicate that 16 participants will be adequate for each experiment. We project recruiting 20 subjects for each experiment to compensate for possible dropouts. A number of subjects will participate in both **SA1** and **SA2** experiments.

Subjects will be recruited from the UMHS Movement Disorders Clinics. The UMHS Movement Disorders clinic follows a population of about 1300 clinically well-defined patients with PD, and evaluates approximately 200 new PD patients per year. Dr. Albin, Co-Director of the UMHS Movement Disorders clinic, will be in charge of subject recruitment. The UM Movement Disorders group is one of the largest in the nation with 13 faculty and actively involved in clinical research. We successfully recruit simultaneously for major clinical trials such as STEADY-PD and other clinical research projects involving complex protocols such a multiple imaging studies. Movement Disorders group faculty work closely on recruitment with all members of the group committed to assisting with recruitment of study subjects. We have a weekly email notification of studies actively recruiting and a well established system for directing patients identified in clinics as potential research subjects to the attention of study coordinators. The Movement Disorders group is expanded this past summer with the addition of 2 additional, primarily clinical, faculty. We also have 2 clinical fellows.

In addition, we will apply to the UM IRB for a waiver of consent for screening and recruitment purposes only. Our study coordinator (SC) will use the electronic medical record (EMR) to screen all subjects scheduled for clinic visits and will maintain a password-protected screening log. The SC will contact possibly eligible subjects by phone in advance of their Neurology clinic appointment—so that subjects can discuss the study with their physician and so that our team can be available at that time to answer any questions—and will introduce them to the study, the ardor and nature of the study procedures, and to review inclusion/exclusion criteria. Subjects who are interested in participating will be scheduled for a baseline testing visit.

If recruitment lags, we will recruit regionally through the Michigan Parkinson Foundation (MPF; see attached letter of support). MPF is the major service organization for PD in Michigan. It supports dozens of local chapters and has a newsletter with circulation in the thousands.

Retention is clearly critical in studies of this type. Our experience with complex studies is reassuring. For multiple PET imaging studies our group has performed, often involving anywhere from 2 – 4 PET studies (plus MRI imaging) and serial evaluations, including follow-up PET studies, we have had little difficulty with retention. Dropout rates are <10%. Our study plan budgets for potential dropouts. To enhance retention, our SC will contact subjects via phone on a regular basis throughout the period from study entry to completion. This type of personal contact is usually effective in maintaining study participation. We will provide reimbursement for travel expenses and a modest volunteer fee on study completion.

Inclusion Criteria: PD diagnosis will be based on the recent Movement Disorder Society criteria.

a) PD subjects >45 years and <81 will be studied.
b) H&Y1-2 (early PD) subjects will be recruited.
c) Only subjects about to initiate treatment with L-dopa preparations will be enrolled.

Exclusion Criteria:

a) The presence of other neurologic disease or neurologic findings on examination.
b) Cognitive Impairment: Montreal Cognitive Assessment (MoCA) score <24.
c) Depression: Geriatric Depression Scale (GDS) score >5.
d) Use of dopamine agonists or stimulants.
e) Evidence of a stroke or mass lesion on prior structural brain imaging (CT or MRI).
f) Evidence of any confounding medical or psychiatric problem that would preclude task participation.

Sources of Materials:

Information gathered specifically for this research project includes test results from clinical test scales, standardized neuropsychological measures and from experimental cognitive tests, neurobehavioral rating scales, clinical motor data, questionnaires, standardized interview, and data derived from structural and functional MRI.

Potential Risks:

Confidentiality of Research Information: The research data to be collected from subjects will consist of confidential information relating to clinical, neuropsychological, mood, neuroanatomical, and neurochemical functions. These research data are not intended for entry into the subjects' clinical medical records. However, the data remain potentially discoverable. This may lead to violation of privacy and embarrassment of the subject.

Clinical and Behavioral Testing: Risks in regard to the behavioral assessment are limited to fatigue, frustration and momentary embarrassment that may occur when one experiences difficulty disclosing information or during task performance. The overnight "off" state may result in discomfort and transient worsening of parkinsonism symptoms.

Adequacy of Protection Against Risks:

Recruitment and Informed Consent:

Subjects will be recruited from the UM Movement Disorders clinic and by advertisement. Individuals willing to participate will be scheduled for the research procedures at which time the nature and risks of the procedures will again be review d with the subjects and a written informed consent form will be obtained by one of the study investigators. One copy of the signed consent form will be given to the subject, one will be placed in the patient's medical record and a third will be kept in the patient's study binder kept at the patient's research site. Study visits will be conducted in Dr. Lee's laboratory in East Hall at the University of Michigan.

Protection Against Risk:

Confidentiality of Research Information: The possibility of unintended disclosure of medical or research data is minimal, but not entirely impossible. We will employ stringent safeguards against unintended and inappropriate discovery and dissemination of personal medical and research data in our subjects by a multi-layered approach. All data bearing potential subject identifiers will reside solely in locked files in the offices of the study investigators. Original data collection documents will be maintained in secure files under the control of the investigators. Entries regarding details of the research project and its results will not be submitted to clinical medical databases. Electronic databases in the project will employ subject codes that cannot be linked directly to participants without a "key", possessed only by the study investigators in a secure location, and maintained separately from the databases. Databases will be housed on protected UM servers. Personal information that would directly identify study subjects will not be used in any publications or presentations resulting from this research study, unless separate written permission is given by the subject (or proxy). Any superfluous records will be shredded.

Clinical and Behavioral Testing: Care will be taken to minimize distress. The study protocol is designed with the minimum number of procedures and tasks, so as to minimize participant burden. Subjects will be addressed in a courteous manner that does not infringe the patient's dignity. These individuals are prepared to respond to patient anxiety, concern and other behavioral changes as appropriate to the situation. Offering breaks and

reassuring subjects will further minimize risks when necessary. All study visits will occur in the morning. Subjects studied in the overnight "off state" will take their medication as soon as study procedures are concluded.

E. Safety Monitoring:

Review of study procedures and adverse effects will be performed on a monthly basis. The PI will be responsible for monitoring any break in confidentiality and for reporting any adverse events following University of Michigan IRB guidelines. For purposes of this study, an AE is defined as any unfavorable or unintended change in structure, function, signs, or symptoms temporally associated with participation in this study, whether or not a causal relationship with the study has been established. Clinically significant abnormalities may be considered an AE if deemed appropriate by the PI. Unexpected worsening of a pre-existing condition is also considered an AE, as is the discovery of an abnormal finding during physical exam that was not included in the medical history. Breaches of confidentiality will be considered related to the research whenever they occur and will be reported. Withdrawals from the study and the reason for these withdrawals will also be reported.

The PI and Co-I are in daily contact with the project research staff testing the participants, scoring and entering data, and will monitor their procedures to ensure that confidentiality is maintained. The PI will ensure that the IRB is notified of any adverse event following the IRB guidelines. Expected and unexpected serious (including fatal) adverse reactions and major unresolved disputes between the research investigator(s) and the research participant or between research investigator(s) will be expeditiously reported to the IRB of the University of Michigan. At the time of renewal, the IRB will be provided with a summary indicating the frequency of the monitoring, cumulative adverse event data, information regarding participant safety or ethics changes, confidentiality issues, benefit-to-risk changes and recommendations on continuing, changing or terminating the study.

For independent oversight, Dr. Kelvin Chou, a Movement Disorder neurologist with considerable trial experience, will act as a DSMB. Dr. Chou will meet with the study team to review the protocol prior to study initiation, 6 months after study initiation, and then yearly. Dr. Chou will receive a study charter that empowers him to recommend significant study changes, including study termination. All AEs will be immediately communicated to Dr. Chou for review.

Definitions:

An Adverse Event is any undesirable experience occurring in a subject during a clinical trial, whether or not considered related to the investigational protocol. For reporting purposes, we will distinguish among pre-existing conditions and trial-emergent adverse events.

Pre-Existing Conditions (i.e., undesirable experiences, signs, or symptoms that begin prior to Study Procedures) will not be reported as adverse events unless they worsen in intensity or frequency after study entry (i.e., satisfy definition of Trial-Emergent, below).

Trial-Emergent Adverse Events are undesirable experiences, signs or symptoms that begin or worsen in intensity or frequency after the Screening Visit, and prior to administration of study drug at the Imaging Visit. These will be reported as adverse events.

Serious Adverse Event: A serious adverse event is an adverse event that is fatal or life-threatening, or results in hospitalization, prolongation of hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. A life-threatening adverse event is an adverse event that, in the view of the investigators, places the subject at immediate risk of death from the reaction, as it occurred.

Unexpected Adverse Event: An unexpected adverse event is an experience not previously reported or an adverse event that occurs with specificity, severity or frequency that is not consistent with the investigator's prior experience with the research methods.

Relationship to Research Protocol: The assessment of the relationship of an adverse event to the study protocol (none, remote, possible, and probable) is a clinical decision based on all available information at the time of resolution or stabilization. The following definitions of the relationship between the study procedures and the adverse event (including serious adverse events) will be considered:

Remote (unlikely, doubtful, improbable): The time course of the study procedure(s) and the occurrence or worsening of the adverse event makes a causal relationship unlikely and another cause is probable.

Possible: The time course of the study procedure(s) and the occurrence or worsening of the adverse event is consistent with a causal relationship, but another cause cannot be ruled out. OR The time course of the study procedure(s) and the occurrence or worsening of the adverse event is not consistent with a causal relationship but no alternative cause can be identified. If the Investigators are unable to assess causality, the adverse event will be considered "Possible" by definition and not "Remote."
Probable: The time course of the study procedure(s) and the occurrence or worsening of the adverse event is consistent with a causal relationship, and no other cause can be identified.
Intensity/Severity of an Adverse Event: In addition to assessing the relationship of the administration of the investigational product/procedure to adverse events, an assessment is required of the intensity (severity) of the event. The following classifications will be used:
Mild: A mild adverse event is usually transient in nature and generally does not interfere with normal activities.
Moderate: A moderate adverse event is sufficiently discomforting to interfere with normal activities.
Severe: A severe adverse event is incapacitating and prevents normal activities. However, a severe event is not necessarily a serious event. Nor must a serious event necessarily be severe.

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