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EDITED BY

Nicola Modugno,
Mediterranean Neurological Institute
Neuromed (IRCCS), Italy

REVIEWED BY

Adriana Galvan,
Emory University, United States
Dawn M. Taylor,
Lerner Research Institute, Cleveland
Clinic, United States

*CORRESPONDENCE

Matthew D. Johnson
john5101@umn.edu

†These authors share first authorship

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Spatiotemporal scaling changes in gait in a progressive model of Parkinson's disease

Alex M. Doyle^{1†}, Devyn Bauer^{2†}, Claudia Hendrix², Ying Yu²,
Shane D. Nebeck², Sinta Fergus², Jordan Krieg³,
Lucius K. Wilmerding³, Madeline Blumenfeld³, Emily Lecy³,
Chelsea Spencer³, Ziling Luo², Disa Sullivan³, Krista Brackman¹,
Dylan Ross², Sendréa Best³, Ajay Verma², Tyler Havel²,
Jing Wang², Luke Johnson², Jerrold L. Vitek² and
Matthew D. Johnson^{3*}

¹Department of Neuroscience, University of Minnesota, Minneapolis, MN, United States,

²Department of Neurology, University of Minnesota, Minneapolis, MN, United States, ³Department
of Biomedical Engineering, University of Minnesota, Minneapolis, MN, United States

Objective: Gait dysfunction is one of the most difficult motor signs to treat in patients with Parkinson's disease (PD). Understanding its pathophysiology and developing more effective therapies for parkinsonian gait dysfunction will require preclinical studies that can quantitatively and objectively assess the spatial and temporal features of gait.

Design: We developed a novel system for measuring volitional, naturalistic gait patterns in non-human primates, and then applied the approach to characterize the progression of parkinsonian gait dysfunction across a sequence of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatments that allowed for intrasubject comparisons across mild, moderate, and severe stages.

Results: Parkinsonian gait dysfunction was characterized across treatment levels by a slower stride speed, increased time in both the stance and swing phase of the stride cycle, and decreased cadence that progressively worsened with overall parkinsonian severity. In contrast, decreased stride length occurred most notably in the moderate to severe parkinsonian state.

Conclusion: The results suggest that mild parkinsonism in the primate model of PD starts with temporal gait deficits, whereas spatial gait deficits manifest after reaching a more severe parkinsonian state overall. This study provides important context for preclinical studies in non-human primates studying the neurophysiology of and treatments for parkinsonian gait.

KEYWORDS

Parkinson's disease, gait, MPTP, non-human primate, pressure walkway

Introduction

Parkinson's disease is characterized by several cardinal motor signs that include bradykinesia, resting tremor, muscle rigidity, and gait and postural control dysfunction (1, 2). Of these motor signs, gait dysfunction is often the most debilitating in terms of quality of life (3–6) and can be the most difficult to treat with dopaminergic drugs or with

deep brain stimulation (DBS) therapy (7–10). Parkinsonian gait dysfunction in humans consists of reduced gait speed, decreased stride length (distance between two consecutive heel steps of the same foot), increased cadence, and variability in gait patterns (10–12).

Given the clinical need for more robust treatments of parkinsonian gait dysfunction, further study is needed to better understand the pathophysiology of parkinsonian gait (13) and the neurophysiological changes (14) that occur within the brain with treatments that improve one or more aspects of parkinsonian gait. Animal models of PD provide an opportunity to not only explore brain circuits underlying parkinsonian gait deficits but to also investigate and further develop new therapies for treating these deficits (15, 16). Rodent studies have demonstrated that 6-OHDA and MPTP treatments induce shorter stride lengths (17–20), increased time in the stance phase, and decreased time in the swing phase (17, 19, 20). Studies looking at dynamic components of gait have also found increased variability in gait measures (17, 19) and asymmetry of gait (21).

The systemic MPTP model of PD in aged non-human primates (NHPs) has been shown to mimic many of the gait deficits observed in human PD including decreased gait speed, stride length, and stride speed (22–24). To date, analysis of gait dysfunction in this animal model of PD have included subjective ratings through motor-sign criteria based on clinical rating scales (25–27) or video analysis of subjects walking while being guided using a pole-and-collar system (22, 23). Additional investigations include NHPs in a non-PD state that have been trained to walk bipedally on a treadmill while restrained within a recording apparatus to investigate neuronal activity in the brainstem during gait (28). While much has been discovered from these studies, natural ambulatory behavior for NHPs is quadrupedal walking (29, 30) without physical restraint. To that end, a recent study adapted a commonly used murine automated gait analysis stem to quantify commonly studied gait parameters in parkinsonian marmosets (31). However, there remains a need to investigate natural ambulatory behavior and how gait dysfunction evolves with increasing parkinsonian severity.

Clinical studies investigating parkinsonian gait often provide quantitative analysis of gait parameters using, for example, a pressure walkway system enabling unrestricted ambulation between spatial locations (32–36). Such an approach allows one to quantify gait initiation and turning, which are known to be affected in PD (37, 38). Rodent studies have utilized similar quantitative gait analysis methods including optical imaging of a glass walkway plate to capture the static and dynamic components of gait and pressure intensity of limb contacts (20, 39). Developing a similar quantitative approach for parkinsonian NHPs would enable future studies to dissect the cortical and subcortical pathophysiological changes that underlie parkinsonian gait dysfunction and to investigate targeted treatments including DBS therapy.

TABLE 1 Summary of MPTP dosing over time.

Subject	Mild parkinsonism			Moderate parkinsonism			Severe parkinsonism		
	Cumulative dosage (mg/kg)	# of injections	Period (days)	Cumulative dosage (mg/kg)	# of injections	Period (days)	Cumulative dosage (mg/kg)	# of injections	Period (days)
A	1.7	6	2	2.3	2	2	.	.	.
B	1.1	4	36	3.9	12	98	12.14	31	252
N [‡]	.	.	.	1.2	1	1	0.8	2	2

[‡] An MPTP injection induced moderate parkinsonism in Subject N bypassing the mild parkinsonian state. Doses for subject A (seven injections 0.3 mg/kg, one injection 0.23 mg/kg), subject B (27 injections 0.2 mg/kg, 14 injections 0.3 mg/kg, and six injections 0.4 mg/kg), subject N (three injections 0.4 mg/kg). Cumulative MPTP dosage, number of injections, and time period needed to reach each parkinsonian state. Cells with “.” indicate unavailable data.

In this study, we developed a novel testing apparatus to quantitatively assess gait parameters of freely-ambulating NHPs. We describe quantitative spatiotemporal analysis of changes in gait parameters across multiple severity levels of parkinsonism in the MPTP-treated NHP model of PD. These quantitative changes were then compared and evaluated in the context of known gait dysfunction parameters in human PD.

Methods

Animals

Kinematic gait data were collected from three adult female rhesus macaques (*Macaca mulatta*; Subject A: 24 yrs. old, 10 kg; Subject B: 23 yrs. old 12 kg; Subject N: 16 yrs. old, 11 kg). Animal care complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and all behavioral protocols were approved by the University of Minnesota Institutional Animal Care and Use Committee.

MPTP administration

To investigate gait parameter changes between naïve and parkinsonian states, all subjects were rendered parkinsonian with systemic intramuscular injections of MPTP (Sigma-Aldrich and Toronto Research Chemicals, ~0.2–0.4 mg/kg per dose) (40–43). MPTP cumulative dosage and injections for each parkinsonian state is documented in Table 1. The mild, moderate, and severe parkinsonian states were quantified by assessing the severity of parkinsonian motor signs using the modified Unified Parkinson's Disease Rating Scale (mUPDRS) (44–46) (Figure 1). The motor sign categories included bradykinesia, akinesia, rigidity, tremor, and axial motor control dysfunction and were evaluated on a scale from 0 to 3 in the 5 subscore categories with three being severely affected. Axial motor scores were calculated as an average rating of gait, posture, balance, and turning dysfunction. Total mUPDRS score ranges for the mild (1–5), moderate (5–10), and severe (10–15) PD states were scaled from previously published ranges containing more categories (40–43).

Gait testing apparatus

Gait dysfunction following MPTP treatment was evaluated with a novel Gait Testing Apparatus (GTA). The GTA was fabricated from T-slot aluminum framing and polycarbonate paneling (80/20, Inc.) (Figure 2A). The apparatus consisted of a 2.43 m long tunnel (0.73 × 0.73 m cross-section) capped by two end enclosures (0.76 × 0.76 m cross-section) each equipped with a hopper to provide a food or juice reward. The tunnel contained

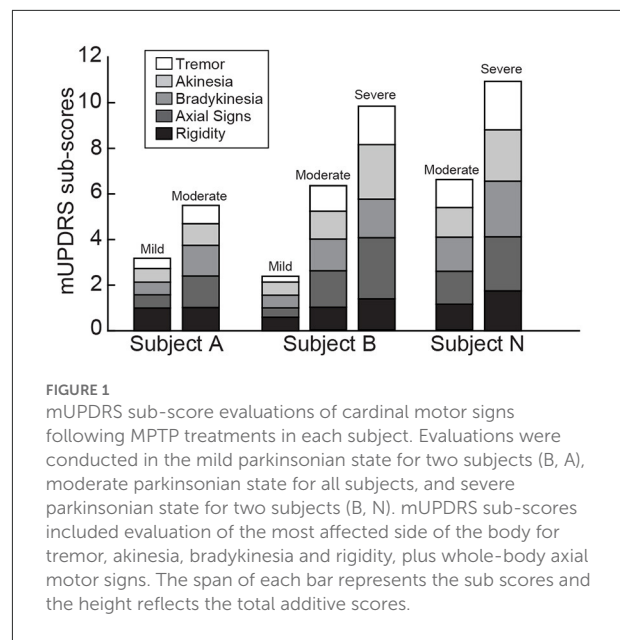


FIGURE 1
mUPDRS sub-score evaluations of cardinal motor signs following MPTP treatments in each subject. Evaluations were conducted in the mild parkinsonian state for two subjects (B, A), moderate parkinsonian state for all subjects, and severe parkinsonian state for two subjects (B, N). mUPDRS sub-scores included evaluation of the most affected side of the body for tremor, akinesia, bradykinesia and rigidity, plus whole-body axial motor signs. The span of each bar represents the sub scores and the height reflects the total additive scores.

a 1.95 × 0.45 m pressure walkway mat (HR Walkway 4 VersaTek system, Tekscan, Inc.) with 33,408 evenly distributed pressure sensing cells using resistive sensor technology (4 sensels/cm²) (Figure 2B). The pressure walkway mat was calibrated to the subject's weight prior to each recording.

Data collection

The subjects were acclimated to the GTA and trained to walk (pass) from one turning enclosure to the other for a food or juice reward. A minimum of five experimental sessions (each conducted on different days) with at least 15 successful passes were collected in the naïve state and as many passes as possible in the subsequent parkinsonian states. A successful pass was defined as the primate walking on all limbs from one enclosure to the other without stopping, turning, exhibiting excessive hesitation, or other non-continuous ambulating behaviors within the walkway. Data collection began when the subject contacted any pressure walkway sensors and stopped when the subject left the walkway. Pressure data from the walkway was digitized at 30 frames/s. Concurrent video recordings captured the profile view of the walkway.

Data processing

"Strike-boxes" (Figure 2B, rectangle circumscribing the perimeter of each limb print) were manually placed within Tekscan software (Tekscan Walkway 7.66, Tekscan Inc.) and delineated the recorded pressure data (kPa) for each limb. This

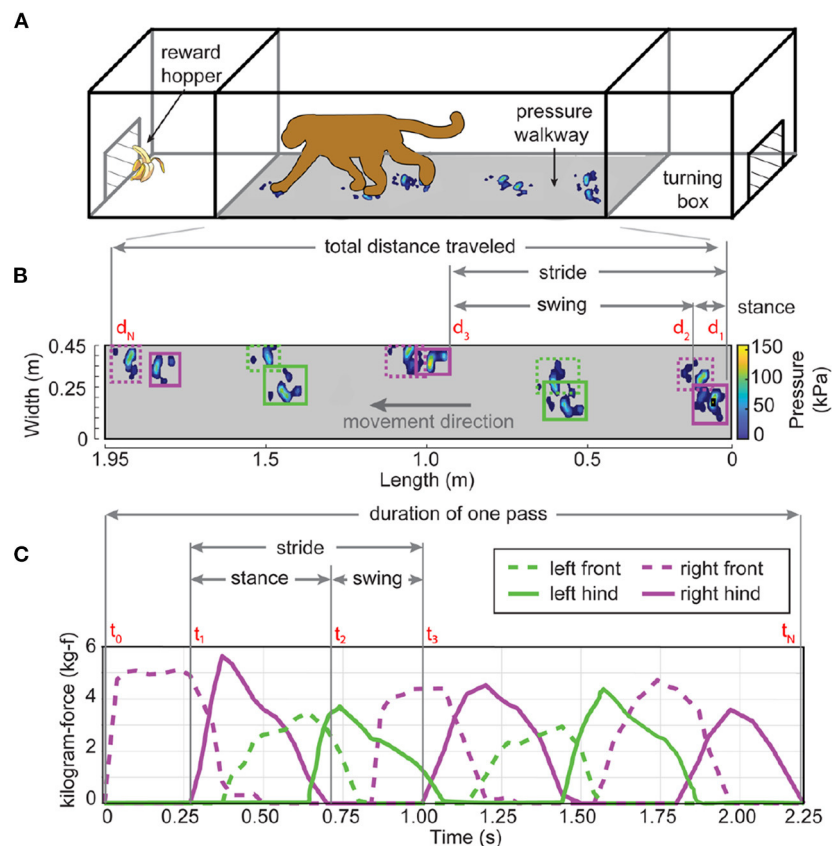


FIGURE 2

Gait testing apparatus and spatiotemporal analysis of gait parameters. (A) The GTA consists of a tunnel capped at each side by end enclosures with sliding doors (not shown). A pressure mat (gray shaded area) recorded location, time, and magnitude of contact pressure (pixelated blue hand and foot prints). Food or juice reward was delivered through hoppers in each end enclosure. (B) Overhead perspective of pixelated calibrated pressure data (color bar, kPa) recorded for a representative pass/trial from right-to-left. Post-processed 'strike-boxes' placed around each hand or foot print identified contact points and pressure magnitudes by limb (front/hind limbs shown as dashed/solid lines, respectively, and left/right sides shown in green/purple, respectively). Interlimb distance is the length between leading edges of consecutive ipsilateral limb "strike boxes". (C) Time series of the aggregate pressure data converted into kilogram-force (kg-f) captured within each 'strike-box' defined temporal gait parameters and stance force profiles for each limb. The representation of the first stance, swing, and stride progression shown from right-to-left (B) is the same instance shown from left-to-right in the time series. Time and distance variables (red) are illustrated for each gait parameter, see Table 2.

allowed for extraction of limb-specific spatiotemporal pressure data, which were exported to MATLAB (MathWorks). Custom scripts were used to calculate stance-swing phases, cadence, and gait speed. For each limb, individual stance and swing length (m) were defined by the distance within and between 'strike-boxes', respectively (Figure 2B). Stride length (m) was the sum of the distance between consecutive stance and swing phases. Time series data of the aggregate pressure profiles (kPa) converted to kilogram-force (kgf), within and between 'strike-boxes', defined the temporal components of gait (Figure 2C). Specifically, stance time (s) was defined as the time between the first and last instance of non-zero pressure mat data within a "strike-box". Swing time duration was the time (s) between consecutive stances when pressure was not detected. Stride time was the sum of consecutive stance and swing times for each limb.

Interlimb length was the distance between the placement of the digits of the front limb and the placement of the digits of the ipsilateral hind limb. Partial hand or footprints ($< \sim 3/4$ size) near the end enclosures during the first and last stances in a pass/trial were excluded from further analysis. Additionally, the presence of a momentary pressure anywhere on the mat limited to two consecutive data frames or less (i.e., $< \sim 67$ ms) were considered noise or incomplete stances and excluded from further analysis.

Cadence, or step rate (steps/min), was defined as the number of stances (i.e., "strike-boxes" for all limbs) within a single pass/trial divided by the trial duration and then converted into steps/min. Gait speed was defined as the distance traveled (i.e., heel-to-toe distance between the first and last "strike-box" in a trial, regardless of limb) divided by the duration of the trial. A representative example of how these various

TABLE 2 Definitions of spatial and temporal gait parameters.

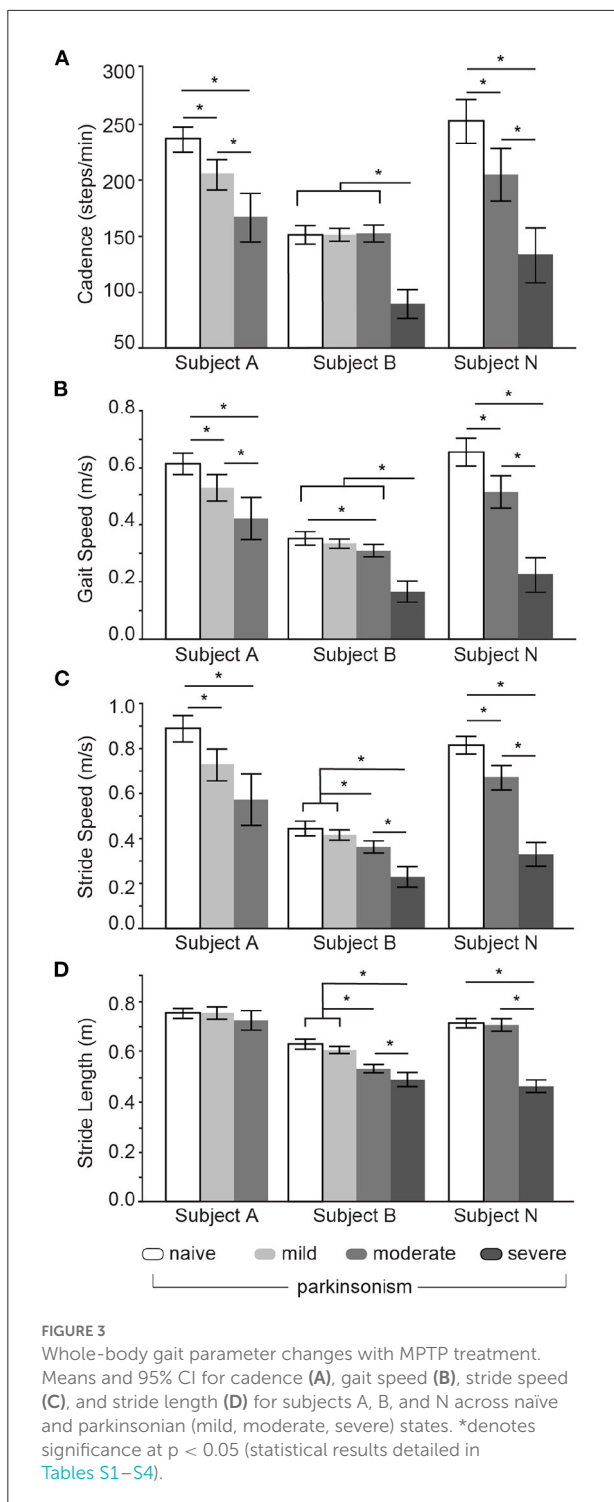
Gait Variable	Definition
Gait Speed	The speed of one pass. The distance traveled between the heel edge of the first strike box to the toe edge of the last strike box divided by the time of the first instance of non-zero pressure data of the first strike box to the time of the last instance of non-zero pressure data in the last strike box.
	$\frac{d_N}{t_N}$ meters per second (m/s)
Cadence (steps/min)	Step rate per pass. The number of stances within a single trail divided by trail duration and converted into steps/min.
	$\frac{\#Stances * 60 (seconds/minute)}{t_N}$ steps per minute (steps/min)
Stride Length	The distance between two consecutive contacts of one limb (Left front heel to left front heel). The distance between the edge of the strike box closest to the heel and the edge of the next strike box closest to the heel.
	$(d_3 - d_1)$ meters (m)
Stride Time	The time between two consecutive contacts of one limb. The summation of swing time and stance time
	$(t_3 - t_1)$ seconds (s)
Swing Length	The distance the limb travels “in the air” during a stride. The distance between strike-boxes.
	$(d_3 - d_2)$ meters (m)
Swing Time	The time the limb travels while not in contact with the ground. The time between two consecutive stances when pressure was not detected.
	$(t_3 - t_2)$ seconds (s)
Stance Length	The length of a footprint. The length of the strike box.
	$(d_2 - d_1)$ meters (m)
Stance Time	The time the limb is on the ground. The time between the first and last instance of non-zero pressure mat data within a ‘strike box’.
	$(t_2 - t_1)$ seconds (s)

measures of gait were obtained during a single right-to-left pass is shown in [Figure 2B](#), with a total of 10 step force profiles (i.e., 10 stance “strike-boxes”) over a distance traveled of ~ 1.90 m ([Figure 2B](#)) and a trial duration of 2.25 s ([Figure 2C](#)). The overall cadence and gait speed for the representative pass were 267 limb steps/min (10 stances/2.25 sec \times 60 sec/min) and 0.84 m/s (1.90 m/2.25 sec), respectively.

Statistics

Within-subject behaviors were compared using a mixed model with parkinsonian “state” as fixed and ‘session nested within state’ as random effects. Baseline gait parameters in

the naïve state were compared across subjects using a fixed effects model with “subject” as fixed and “sessions nested within subjects” as random effects. In both models, significant main effects with more than two levels were further analyzed using a Tukey *post-hoc* test. A Levene’s test for homogeneity of variance performed on swing time and length data assessed the change in variability across states. Statistical analyses were conducted in JMP (v15.2.0, SAS Institute) using standard least squares regression. Bar plots showed the least-square means (means calculated from the model) and 95% confidence intervals (CI) of the least-square means (range of 95% of the data). Bar plot 95% CIs should only be compared within animal subplots and not across animal subplots. For brevity, these values will be referred to as “means” and “95% confidence intervals of the



mean” throughout the paper. Effect sizes were calculated from the least-square means and standard error from the mixed and fixed effects models using Cohen’s d for unequal sample sizes and standard error. An effect size value of <0.35 was considered

a “small” effect size, 0.35–0.65 was considered “medium”, and over 0.65 was considered “large”.

Results

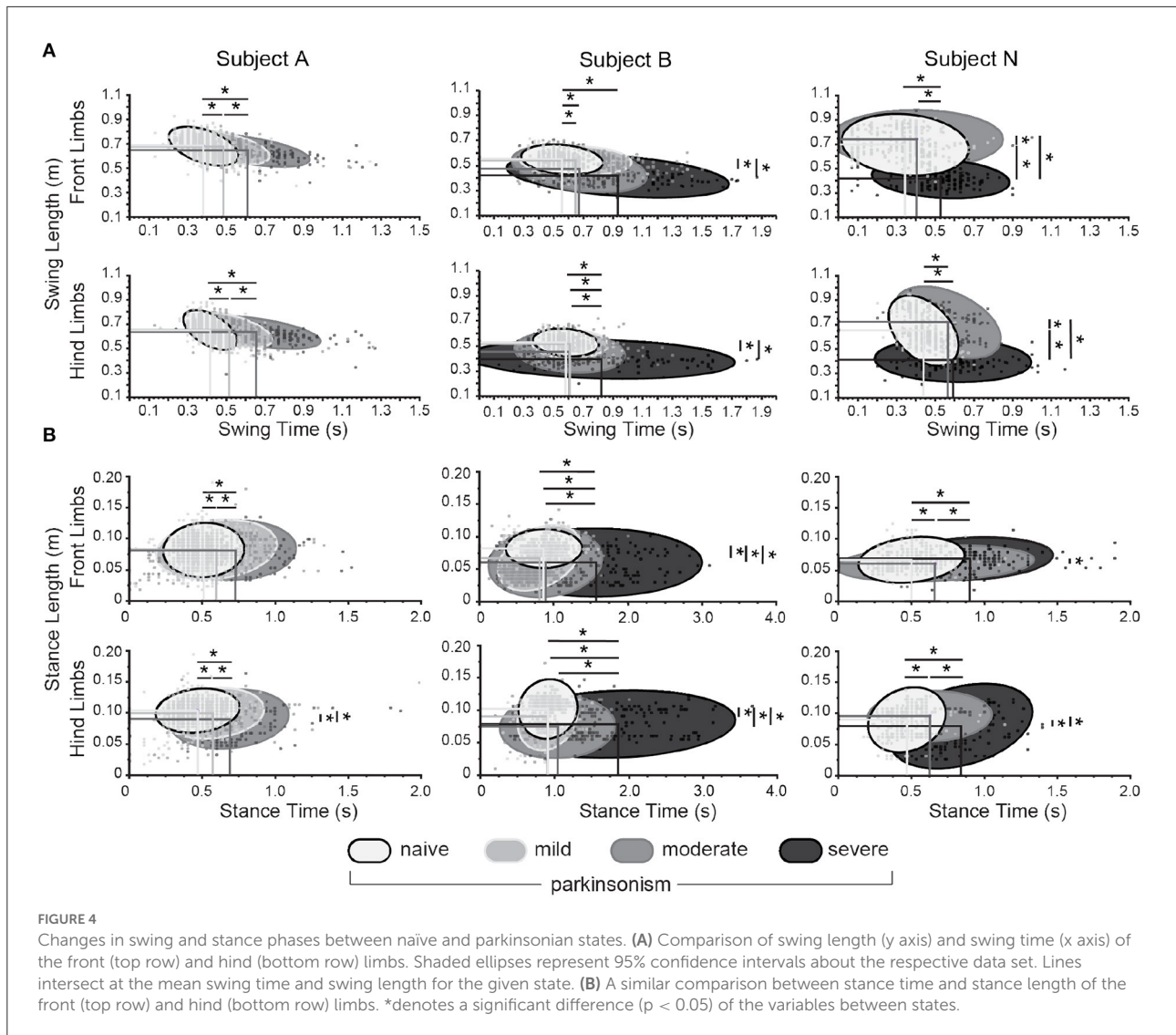
Dataset and observed behaviors

All subjects were brought from a naïve state to a moderate parkinsonian state with repeated injections of MPTP. Two of the subjects (B and A) were evaluated in a mild parkinsonian state, and two subjects were also assessed in a severely parkinsonian state (B and N) (Figure 1, Table S1). Compared to the naïve state, parkinsonian subjects showed less motivation to perform the task, less curiosity to the environment around them, and slower turns or changes in behavior. The observed change in motivation and ability to complete the task with increasing parkinsonian severity was reflected in the average number of passes per session from 21.7 (naïve 823 passes/38 sessions; mild 673 passes/31 sessions) to 10.9 (moderate 261 passes/24 sessions) to 6.2 (severe 62 passes/10 sessions) with increasing parkinsonian severity (Table S1, bottom row).

Coordinated gait parameter changes with MPTP treatment

Similar to humans, each subject had unique gait metrics in the baseline (MPTP naïve state; Figure 3). Subject B baseline (naïve) behavior, in particular, was considerably slower as evidenced by lower cadence, gait speed, and stride speed when compared to the other subjects in the naïve state (Figures 3A–C, white bars). The slower cadence and gait speed for subject B could not be attributed to subject body size (10, 12, 11 kgs) or age (24, 23, 16 yrs) differences amongst subjects (A, B, and N, respectively). Baseline stride length differed across subjects with longest-to-shortest stride lengths for Subject A, N, and then B (Figure 3D, white bars), but the effect size was small (Table S2). Similarity in subject size, age, and stride length support the behavioral observation that subjects A and N had a higher motivation to complete the trials compared to subject B.

Gait metrics in the naïve state steadily decreased across the parkinsonian states. Subjects A and N had significant and progressive decrements in cadence and gait speed across all parkinsonian states, whereas subject B showed either small or no changes until the moderate or severe state for cadence and gait speed (Figures 3A,B, Table S2). Stride speed and stride length for each limb were averaged within each subject and within the naïve and parkinsonian states (Figures 3C,D, respectively). All subjects exhibited slower strides across the mild, moderate, and/or severe states (Figure 3C, Table S2), aligning with an overall slowing of gait with overall increasing parkinsonian severity. In terms of stride length, there was no change in



subjects A or N between the naïve and moderate states and a relatively small, but statistically significant decrease in subject B (Figure 3D, Table S2). Statistically significant and robust decreases in stride length were observed in both subjects (B, N) that reached the severe parkinsonian state.

Stride-by-stride spatiotemporal limb dynamics

To further investigate gait parameter changes with MPTP treatment, the swing and stance phases of individual strides were analyzed and compared between front and hind limb groupings. A total of 13,776 strides (Table S1) were analyzed across the three subjects in the naïve and parkinsonian states. Mean swing time (horizontal axis in Figure 4A) consistently and significantly increased for both front and hind limb groupings

across parkinsonian states (see details on statistical tests and results in Table S3). In addition, the effect sizes of swing time were larger (medium or large) in the naïve to moderate/severe states than in the naïve to mild state (small) (Table S3).

Subject A showed no change in swing length (vertical axis in Figure 4A), and Subject B showed a decrease in swing length in the moderate and severe parkinsonian state with a predominantly medium effect size (Table S3). Subject N showed a decrease across all parkinsonian states with small and medium effect sizes in the moderate state and large effect sizes in the severe state (Table S3). There was also an increase in swing length and swing time variability as the subjects became more parkinsonian, as shown in Figures 4A,B by the elongation of the 95% CI ellipse in both the x- and y-direction. The increase in variance of the swing time and length was confirmed using the HOV Levene’s test on aggregate limb data per subject across parkinsonian states (Table S4).

Mean stance time, shown on the horizontal axis in [Figure 4B](#) significantly increased for both front and hind limb groupings across parkinsonian states for subjects A and N. Most of the effect sizes were small in the naïve to mild and moderate states, and large in the naïve to severe state ([Table S3](#)). Mean stance length (vertical axis in [Figure 4B](#)), decreased in all parkinsonian states for subject B for the front and hind limbs, in the hind limbs in the moderate state for subject A, and in the moderate and severe State for subject N ([Table S3](#)). With the exception of subject B in the naïve to moderate state, these effect sizes were all small ([Table S3](#)).

Discussion

This study used a novel testing apparatus to quantitatively measure volitional, naturalistic gait patterns in a preclinical MPTP non-human primate model of Parkinson's disease. The apparatus, containing a pressure walkway system comparable to those used in human studies, enabled characterization of changes in gait patterns across multiple stages of parkinsonism to identify when and to what extent spatial and temporal features of gait dysfunction occur relative to other cardinal motor signs of PD. Here, we show that NHP subjects exhibited progressive bradykinetic gait driven by a slowing of movement speed, stride speed, and increased time spent in the swing and stance phases of a stride cycle. Robust changes in stride length, on the other hand, were observed primarily in the severe parkinsonian state. Additionally, there was an increase in the variability of gait parameters with increasing parkinsonian severity.

The gait testing apparatus for assessing gait dysfunction

This preclinical study identified high resolution changes in the spatial and temporal dynamics of gait during volitional ambulation in naïve and MPTP-treated NHPs. Prior preclinical studies investigating unconstrained walking have been limited to step-by-step spatial components of gait ([18, 47](#)), temporal measurements of gross coordinated gait behaviors ([22, 23, 48](#)), and video analysis for kinetic estimation of limb dynamics ([22, 23, 49, 50](#)). Murine studies have utilized methods such as optical imaging and ventral plane videography to not only evaluate the static and dynamic components of gait but to assess gait variables similar to those found in the human PD literature, such as base of support length, three point support (similar to double support time in bipeds) ([20](#)), and deficits in footprint intensity contralateral to the lesioned side to evaluate gait asymmetry ([21](#)). There is one study in marmoset NHPs using an automated method to measure footfalls and quantify base of support and interlimb coordination variables ([31](#)). Similar to this study, the GTA can be used in larger

NHPs to quantify complex gait dynamics with precise spatial and temporal resolution. Analyzing pressure dynamics across limbs of one severe parkinsonian subject, a difference between footprint patterns, and thus disordered gait, could be ascertained in this study. Additionally, though not addressed in this current study, this approach has the potential to measure shifting of pressure dynamics within and across limbs when assessing balance and postural instability, anticipatory postural adjustments, festination (i.e., smaller but quicker steps), turning, gait initiation, and freezing of gait.

Comparison of MPTP gait dysfunction to human PD

The most prominent sign of gait dysfunction in PD is reduced stride length ([51, 52](#)). This impaired ability of humans with PD to modulate the amplitude of their stride is thought to be the primary contributing factor for the reduction in gait speed ([52–55](#)). As observed in prior studies with MPTP treatment in NHPs, severe stage animals, like subjects B and N, had a decreased stride length ([22, 23](#)) with slower movement speed. Here, we show that while stride length can decrease slightly in the mild and moderate parkinsonian states, the largest effect on stride length occurs in the severe parkinsonian state in the MPTP-treated rhesus macaque model.

The temporal characteristics of PD gait typically includes an increase in the time it takes to complete a stride ([56](#)), with more time spent with the feet in contact with the ground ([56, 57](#)) and less time with the feet mid-air ([56, 58](#)). Overall, our subjects showed an increase in stride time and stance time; however, the time spent in the swing phase also increased. Given the decrease in gait speed, stride speed, and cadence, this is suggestive of bradykinetic gait in the NHP as opposed to one characterized by festination that can occur in some human PD cases ([54](#)).

The increase in variability of the swing phase in the parkinsonian animals is consistent with increases in variability in gait parameters found in humans with PD ([12, 56, 59](#)). While gait variability is a measure of disease severity, it is also a metric used in determining the effectiveness of therapies ([60](#)).

Progression of gait dysfunction in the MPTP animal model

The data presented are the result of a within-subjects experimental design that is consistent with prior studies done in this field ([61–63](#)). It is well known that the MPTP NHP model captures many of the electrophysiological and phenotypic changes that occur in human PD ([27, 40–43, 64](#)), but few studies detail the parkinsonian gait deficits. NHPs in the severe state exhibit step/stride length decreases, freezing of gait, postural

deficits, and difficulty turning (22–24); however, there has been little known of stride cycle changes and the appearance of gait dysfunction with increasing parkinsonian severity with NHPs.

The subjects exhibited more prominent bradykinetic gait with increasing parkinsonian severity. This matched the visual observations of subjects in the mild parkinsonian state where the gait deficits were not easily discerned as compared to the moderate or severe parkinsonian state. The GTA enabled parsing out the subtle gait changes that were more defined in later stages. For instance, subject B showed a small change in swing time of the front limbs that became more pronounced in the severe stage. This state could provide insights in the early signs of parkinsonism, as unlike with human PD studies, these gait changes can be combined with neurophysiological recordings to evaluate the pathogenic mechanisms underlying the emerging deficits and perhaps shed light into potential therapy developments for early PD. The more pronounced gait changes in the moderate and severe states are ideal for studies involving testing of novel therapeutics. In addition, the severe state provides a rich dataset for neurophysiological studies that aim to explore asymmetric gait or freezing of gait.

Limitations and future refinements to the GTA approach

One study limitation was investigating parkinsonian gait dysfunction during ambulation in a small set of subjects. However, the relatively consistent results in the temporal gait parameters across subjects suggest that similar gait patterns will likely occur with larger cohorts of subjects. Additional subjects along the parkinsonian spectrum could further characterize subtle changes in spatial gait metrics. While the analysis focused on data collected during continuous ambulation, the GTA system could also be used to capture other gait behaviors such as freezing of gait (24), festination, difficulty turning, and obstacle maneuvering leveraging both the pressure walkway and assessment of joint kinematics through the clear polycarbonate paneling. The approach also facilitates wireless transmission of neural recordings concurrent with pressure walkway and video capture recordings, which will enable future studies to investigate the neurophysiological basis of the temporal and spatial changes in gait with increasing parkinsonian severities.

Conclusion

This study developed a novel, quantitative approach to investigate gait dysfunction in freely-moving non-human primates (rhesus macaques) across a spectrum of parkinsonian severities. Subjects demonstrated progressive bradykinetic gait, whereas stride length changes occurred most robustly upon reaching the severe parkinsonian state. Knowing how gait

metrics change with increasing parkinsonian severity will enable a broad range of translational studies to better elucidate the circuit-based pathophysiology of parkinsonian gait dysfunction (65–67) and evaluate novel pharmacological and deep brain stimulation treatments for parkinsonian gait dysfunction.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding author.

Ethics statement

Animal care complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and all behavioral protocols were approved by the University of Minnesota Institutional Animal Care and Use Committee.

Author contributions

Conceptualization: MJ, AD, JV, DB, and CH. Data curation and formal analysis and visualization: AD, DB, and CH. Funding acquisition: MJ, JV, and LJ. Investigation: AD, SN, SF, JK, LW, MB, EL, CS, DR, DS, SB, YY, AV, TH, JW, LJ, and MJ. Methodology and writing – original draft: AD, DB, CH, and MJ. Project administration and resources: MJ, JV, LJ, and JW. Software: AD, DB, KB, and ZL. Supervision: CH, MJ, JV, LJ, and JW. Writing – review and editing: AD, DB, CH, SN, SF, JK, LW, MB, EL, CS, ZL, KB, DR, DS, SB, YY, AV, TH, JW, LJ, and MJ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2022.1041934/full#supplementary-material>

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