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Objective quantification of arm rigidity in MPTP-treated primates

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ABSTRACT

Rigidity is a cardinal symptom of Parkinson's disease and is frequently used as an outcome measure in clinical and non-human primate studies examining the effects of medication or surgical intervention. A limitation of current rigidity assessment methods is that they are inherently subjective. To better understand the physiological mechanisms of rigidity and how various therapeutic approaches work, a more objective and quantitative method is needed. In this study, an automated arm rigidity testing (ART) system was developed to objectively quantify rigidity while the primate's limb was moved between two user-specified angles. Recordings of normal force versus elbow-angle were categorized according to area and slope. These quantitative measures of rigidity were investigated in three rhesus macaque monkeys treated with 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine and compared with clinical assessment methods. The ART system incorporates electromyographical recordings that can detect and differentiate active from actual resistance. The ART system detected significant changes in rigidity measures following administration of apomorphine or deep brain stimulation of the globus pallidus internus. The most sensitive measures were total area, extension slope, and flexion slope. The ART system provides precise and reliable measures of rigidity that are objective and quantitative.

1. Introduction

Parkinson's disease (PD) motor symptoms in 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys are typically assessed through a clinical examination in which the severity of bradykinesia, akinesia, postural instability, tremor, and rigidity are given a numerical rating based on a trained expert's perception (Chassain et al., 2001; Imbert et al., 2000). This approach is inherently subjective, making it difficult to compare results between different investigators, and often imprecise, limiting the ability to evaluate the relative efficacy of antiparkinsonian drugs or deep brain stimulation (DBS) parameter settings. For example, Imbert et al. (2000) examined the effects of levodopa on MPTP-treated monkeys using eight different clinical rating scales and concluded that rigidity scores among other motor symptoms varied greatly depending on which scale was used.

Muscle rigidity during passive movement of a limb is one Parkinsonian motor sign for which objective and quantitative techniques have been developed for human patients (Caligiuri, 1994; Halpern et al., 1979; Lee et al., 2002; Mak et al., 2007; Patrick et al., 2001; Pinter et al., 1992; Prochazka et al., 1997; Sepehri et al., 2007; Xia et al., 2006; Xia and Rymer, 2004), but have not adopted in the clinical community. Furthermore, little effort has been made to objectively quantify rigidity in non-human primates. Most primate studies currently use a clinician-based assessment, which relies on human manipulation of the affected limb. Such rigidity measures are limited by inter-rater variability, narrow assessment scale ranges, inconsistencies in the amplitude and rate of limb movement, and an inability to separate active resistance from rigidity (Post et al., 2005).

The aims of this study were to develop and build a mechanical device capable of safely moving a non-human primate's arm between two specified angles at constant speed while objectively quantifying upper extremity rigidity by recording resistive forces to the movement. We hypothesized that such a system would provide a more sensitive measurement of rigidity than current clinical assessment methods, and by incorporating measures of EMG activity, one could distinguish active resistance from rigidity. This

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hypothesis was tested in MPTP-treated monkeys before, during, and after injection of apomorphine or during DBS in the globus pallidus internus (GPi).

2. Materials and methods

2.1. Subjects and surgical procedures

Rigidity measurements were performed on three female rhesus monkeys (*Macacca mulatta*, ~15 years of age) treated with MPTP. Monkeys 1 and 3 received unilateral intracarotid injections (i.c.) of MPTP targeting the left and right hemisphere, respectively to induce significant motor impairment on the side contralateral to the injection (Bankiewicz et al., 1986). Monkey 2 was administered systemic intramuscular (i.m.) MPTP injections resulting in bilateral effects. Multiple i.c. or i.m. MPTP injections were given until a stable PD state was achieved based on various behavior tasks. In both the unilateral and systemic injection cases, only the more severely affected arm was tested. Following at least 1 month of behavioral assessment for Parkinsonian motor signs, metal recording chambers were mounted over a pair of craniotomies (Hashimoto et al., 2003). In two primates, a monkey-scaled version of a clinical DBS lead was implanted through one of the chambers into the globus pallidus along a coronal trajectory such that electrode contacts resided in the sensorimotor regions of both external and internal pallidal segments. An implantable pulse generator (IPG) was positioned subcutaneously below the scapulae and connected to the DBS lead through an extension cable. The study was in compliance with *The National Institutes of Health Guide for the Care and Use of Laboratory Animals* (1996) and approved by the Cleveland Clinic IACUC.

2.2. Arm rigidity testing (ART) system

The ART system was designed to quantify upper extremity rigidity in primates. In order to validate inter-laboratory findings, schematics for the ART system are available upon request to other investigators. The rotating component of the ART system is comprised of two custom-built metal frames connected by a hinge joint (Fig. 1). The setup allowed for comfortable and natural upper extremity positioning and forearm rotation between two user-specified angles with a step resolution of 200 steps per degree provided by a DC stepper motor (AS98, Oriental Motor, Torrance, CA). A force transducer (Gamma Model, ATI, Apex, NC) in a custom-built housing was attached to the forearm frame. A Velcro strap, attached to the additional transducer plate, not the force transducer itself, was used to restrain the primate's arm. The experimenter aligned the elbow joint concentric to the ART's axis of rotation.

The ART system recorded forces along the *X*, *Y*, and *Z* axes and torques in the *XY*, *YZ*, and *XZ* planes. This study concentrated on the force normal to the transducer (Fz, 1/40 N resolution), which best reflected the rigidity about the elbow joint by directly opposing the direction of arm rotation (Fig. 2). Fx (parallel to the forearm), Fy (perpendicular to the forearm), and the three torques were minimized by adjusting the location of the elbow joint in relation to the ART system axis of rotation. During each trial, all data (forearm angle, 3 forces, 3 torques, 2 EMG channels, time series, marker channel) were sampled simultaneously at 200 Hz through an external USB-621x data acquisition card (National Instrumentations, Austin TX) and continuously saved to disk via a USB connection to a laptop. Muscle activity was monitored during recording using EMG (Delsys, Boston, MA) electrodes placed on the bicep and triceps muscles after appropriate surface preparation was done to minimize electrode impedance. EMG signals were amplified (10k gain) and recorded directly to a laptop. An EMG threshold was set to 1 V for each Fz cycle. If the threshold was exceeded, the entire cycle was removed; thus, active resistance of the primate did not influence rigidity measures.

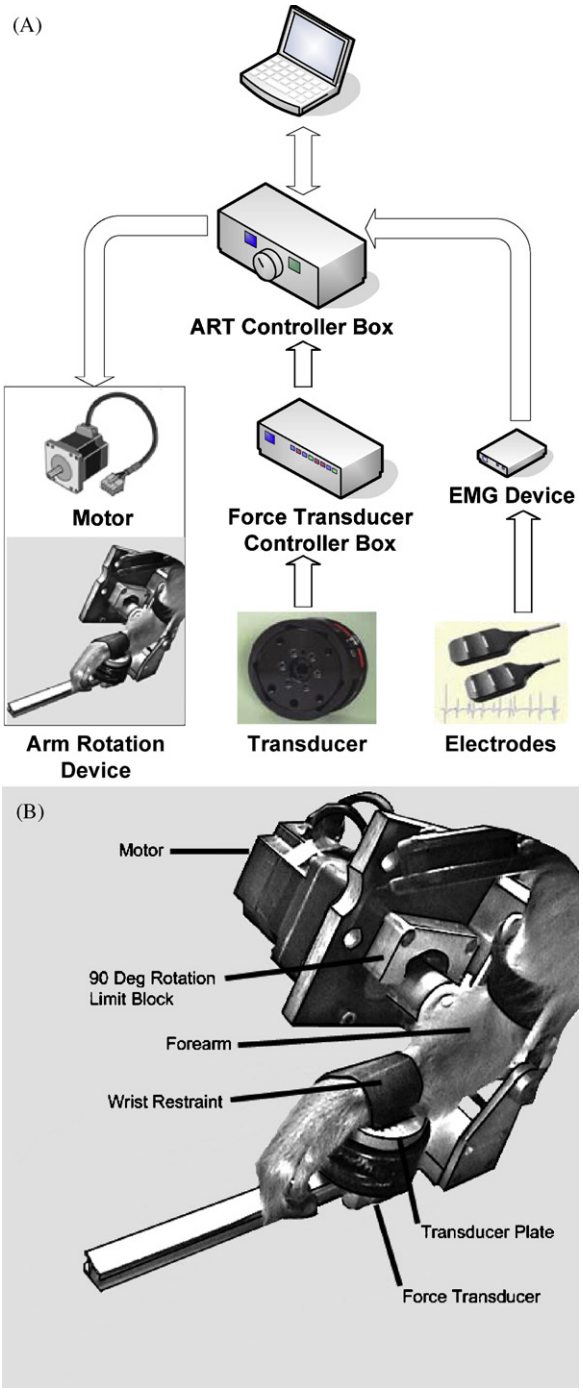

Fig. 1. The ART system was designed to passively flex and extend the subject's arm while recording muscular resistance to that motion. (A) This portable system consisted of an arm rotation motor, force transducer, and EMG recording amplifier, which were all controlled by a custom-built computer software platform in LabView. (B) The arm rotation device comfortably held the monkey's arm with Velcro straps over the distal and proximal arm segments. The elbow joint was positioned along the axis of rotation to prevent torque at the force transducer. The monkey's arm was then flexed and extended between two specified angles. A 100° angle is shown in the image.

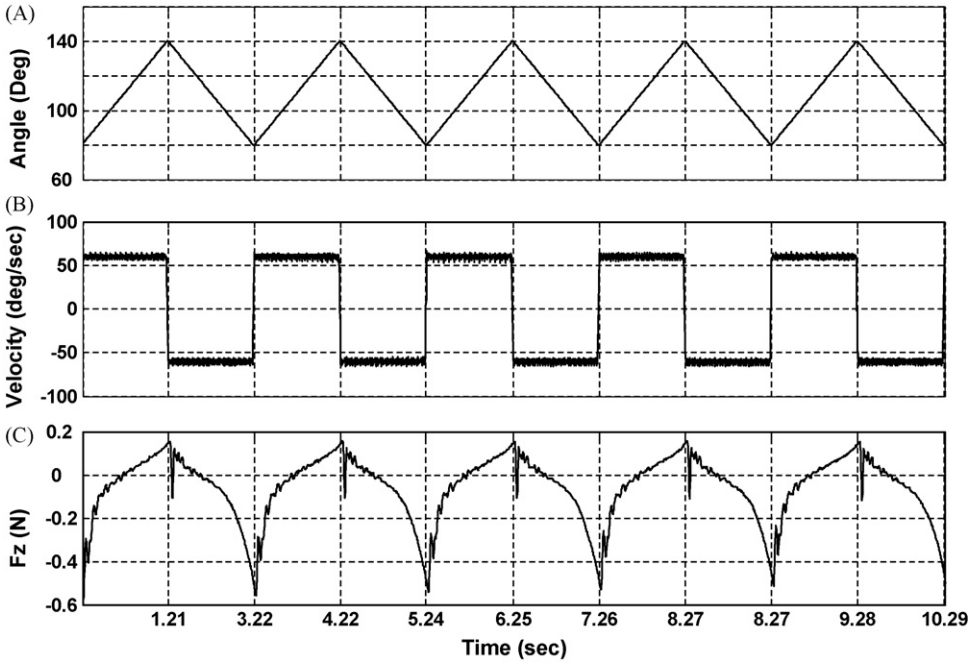

Fig. 2. The ART rotation profile at ~0.5 cycles per second. During extension (80–140°), the force transducer was pulled away from the subject's arm by the rotating lever (+*z* force) whereas during flexion (140–80°), the transducer was being compressed (−*z* force). Rotating velocity was held constant between the two angles such that acceleration was minimized during switching periods between flexion and extension. Response curves include (A) the rotating arm's angle position, (B) the velocity profile sampled at 200 Hz, and (C) time-series of the force normal to the transducer.

A customized software program was developed in LabView to control the movement of the ART system with respect to angle, rate of rotation, and trial duration. A controller box contained the motor driver, National Instruments DAQ USB interface, and additional circuitry for multiple BNC input/output connections. The following safety measures were implemented into the system: emergency stop button directly connected to the motor controller, 90° rotation limit metal bracket, and current overload limit of the motor. Software safety precautions limited the input angle range to 90° and continuously monitored motor lever arm position.

2.3. Clinical assessment of rigidity

Typically with the MPTP-treated monkey model, each primate's rigidity is assessed by the experimenter who extends and flexes the monkey's affected arm to assign a rigidity score based on the perceived resistance to the movement (Imbert et al., 2000). Ratings range from 0 (no rigidity) to 3 (severe rigidity), and in some cases, the evaluator finds it necessary to use fractional increments within the scale. In order to assess the advantages of the ART system, a mock arm was built for fine resistance/rigidity adjustment. Primate clinical rating experts participated in a single blind random study in which they rated rigidity of the mock arm as they would with an MPTP primate. Predetermined rigidity settings were chosen to approximate the 0–3 primate rating scale. Mock arm position was recorded using an Optotrak Motion Capture System (NDI, Waterloo, Ontario) in order to assess rotation velocity.

2.4. Procedures

Monkeys were trained over several months to sit calm and quietly in a primate chair during recording sessions. Transporting the monkey between the housing cages and experiment room was accomplished by restraining the primate in the chair at the waist and neck. The arm of interest was properly positioned in the ART rotating frame. The range of motion between forearm and upper arm was 140° (extended) and 80° (flexed) for monkey 1 and 70–130° for monkeys 2 and 3. Arm angle was derived from the motor step position. The forearm position and velocity profile were configured such that acceleration and deceleration time were minimized. Rotation rate was set to 0.5 cycles per second (60°/s) (Fig. 2B).

Rigidity was assessed under two different therapeutic conditions: systemic apomorphine and targeted GPi-DBS. Apomorphine has been shown to have similar clinical effects to that of levodopa (LeWitt, 2004), but with more rapid onset (Chen and Obering, 2005). After a 5–10 min baseline recording period, an intramuscular (0.08 mg/kg) injection of apomorphine was administered to monkey 1 (unilateral left hemisphere MPTP injection). Force data was collected continuously for 60 mins post-injection. Monkeys 2 (bilateral MPTP injection) and 3 (unilateral MPTP right hemisphere MPTP injection) were assessed with the ART system while ON and OFF GPi DBS. Therapeutic stimulation parameters had been determined previously through clinical examinations. Stimulation parameters consisted of charge-balanced pseudomonophasic pulse trains (135 Hz frequency, 60 μs pulse width) with a peak amplitude of 2 V in monkey 2 (stimulated contacts 2^{-}/Case^{+}) and 3 V in monkey 3 (stimulated contacts $1^{-}/2^{+}$). Force data were continuously collected for 5 min OFF-STIM and then 2 min ON-STIM based on previous DBS testing trials. Manual digital trigger pulses marked the transition between stimulation states.

2.5. Data processing

Angle and Fz data from the ART system were used to characterize rigidity. Initial processing separated Fz time-profiles into individual cycles (extension and flexion). A low-pass Butterworth filter (3 pole, 10 Hz) removed any high-frequency artifacts (Fig. 3). Five

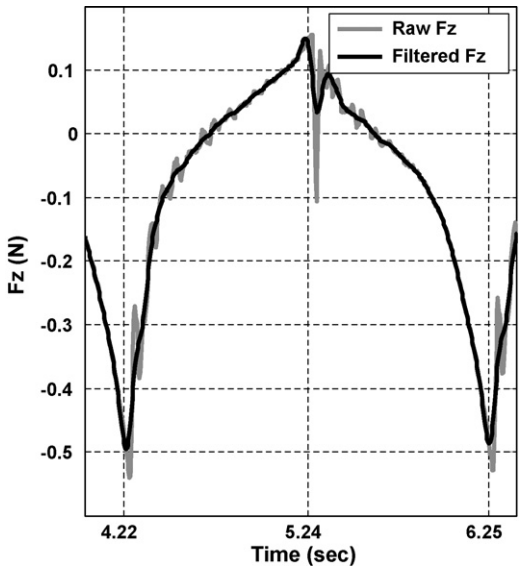

Fig. 3. Force recordings lacking significant EMG activity were filtered to remove high frequency oscillations in order to decrease variability of rigidity measures.

degrees from the extension and flexion angle were excluded from data processing to remove ringing caused by the sudden change in direction of the lever arm during rotation. All data were processed using customized Matlab scripts (MathWorks, Natick, MA, Version 7.4).

2.6. Rigidity measures

Five measures of rigidity were calculated: total area (TA), also referred to as total hysteresis (Sepehri et al., 2007), or the area between the extension and flexion force–angle curves, extension area (EA), flexion area (FA), extension slope (ES), and flexion slope (FS) (Fig. 4). It was reported that PD wrist rigidity differed between extension and flexion (Xia et al., 2006); therefore, area and slope of both movements were calculated.

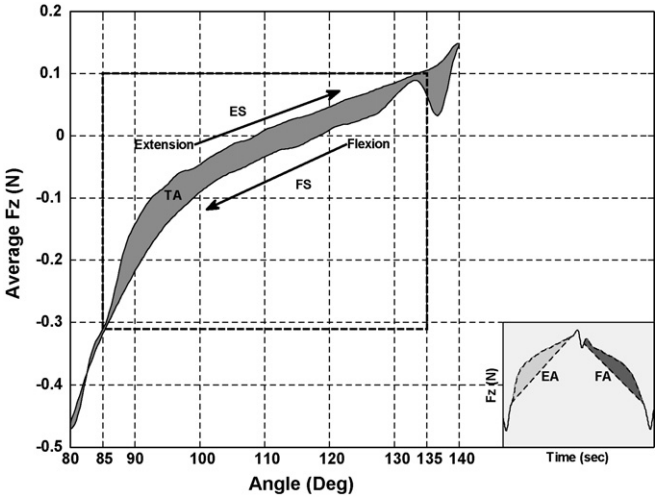

Fig. 4. Rigidity was quantified with multiple analytical parameters on the angle versus Fz plot. Abbreviations include TA: total area, EA: extension area, FA: flexion area, ES: extension slope, and FS: flexion slope. The dashed box, marking the angle boundaries (±5° from fully extended and flexed position) for calculating the rigidity measures, were imposed to prevent biasing parameter estimation with measurements during the switching period between extension and flexion.

2.7. Statistical analysis

Each extension/flexion cycle was considered an independent sample. Calculations for the apomorphine trials and clinical ratings were done using one-way ANOVA with post hoc Tukey tests to compare pre-injection, 3 min post-injection (T1), and 60 min post-injection (T2) time points. The DBS trials compared recorded ON-STIM and OFF-STIM with clinical assessment using two-sample student *t*-tests. All statistical analyses were done with SPSS v14.

3. Results

3.1. ART sensitivity to active resistance

The ART system synchronized sampling of force and EMG signals. Electromyography electrodes applied over the monkey's biceps and triceps provided a systematic approach to detecting active resistance during trials (Fig. 5A). Several changes occurred when comparing raw EMG baseline (relaxed state) to active resistance, which can be characterized by voltage spikes at full extension or flexion proportional to the degree of active resistance and high frequency components. Results also confirm that after muscle activity, EMG and Fz signals returned to baseline levels. Rigidity measures differed greatly when comparing apomorphine data sets with and without active resistance removed (Fig. 5B). When the EMG threshold method was disabled, variance was significantly greater and mean rigidity values were overestimated.

3.2. Mock arm rigidity testing with ART system and human experimenter

The mock arm provided a controlled system with reproducible rigidity settings. The ART system was highly sensitive to small changes in resistance throughout the mock arm rigidity spectrum (Fig. 6A). The evaluator's ability to distinguish rigidity settings was most sensitive between resistances 2 and 3 whereas intra- and inter-rater reliability was compromised at low and high mock rigidity settings (Fig. 6B). Further data analysis showed a large variance in mock arm velocity (37 ± 29 mm/s) during these trials.

3.3. Changes in rigidity following apomorphine

The ART system's sensitivity and stability to apomorphine were evaluated by recording continuously for 60 min after a systemic injection. Specifically, these experiments tested (1) whether the system could detect a decrease in rigidity due to apomorphine, (2) which rigidity measures best accounted for these changes, and (3) how these responses changed as the effects of apomorphine dissipated. Changes in the force waveform were evident when plotted versus time (Fig. 7A) where the Fz amplitude at the extended and flexed angles decreased at '3 min post-injection' and recovered at '60 min post-injection'. Area and slope followed a similar trend when plotted versus angle (Fig. 7B). Following the administration of apomorphine, all rigidity measures except FA ($F_{2,143} = 118.3$) decreased significantly ($p < 0.01$). Total area ($F_{2,143} = 290.9$) exhibited the largest percent drop (71%) relative to baseline pre-injection while ES ($F_{2,143} = 398.1$) and FS ($F_{2,143} = 337.7$) exhibited the largest percent recoveries (90.5% and 87.5%, respectively). EA ($F_{2,143} = 216.2$) and FA exhibited irregular behavior during apomorphine injection. EA exhibited only a 26.4% drop, and FA increased by almost double at T1 (Fig. 7C).

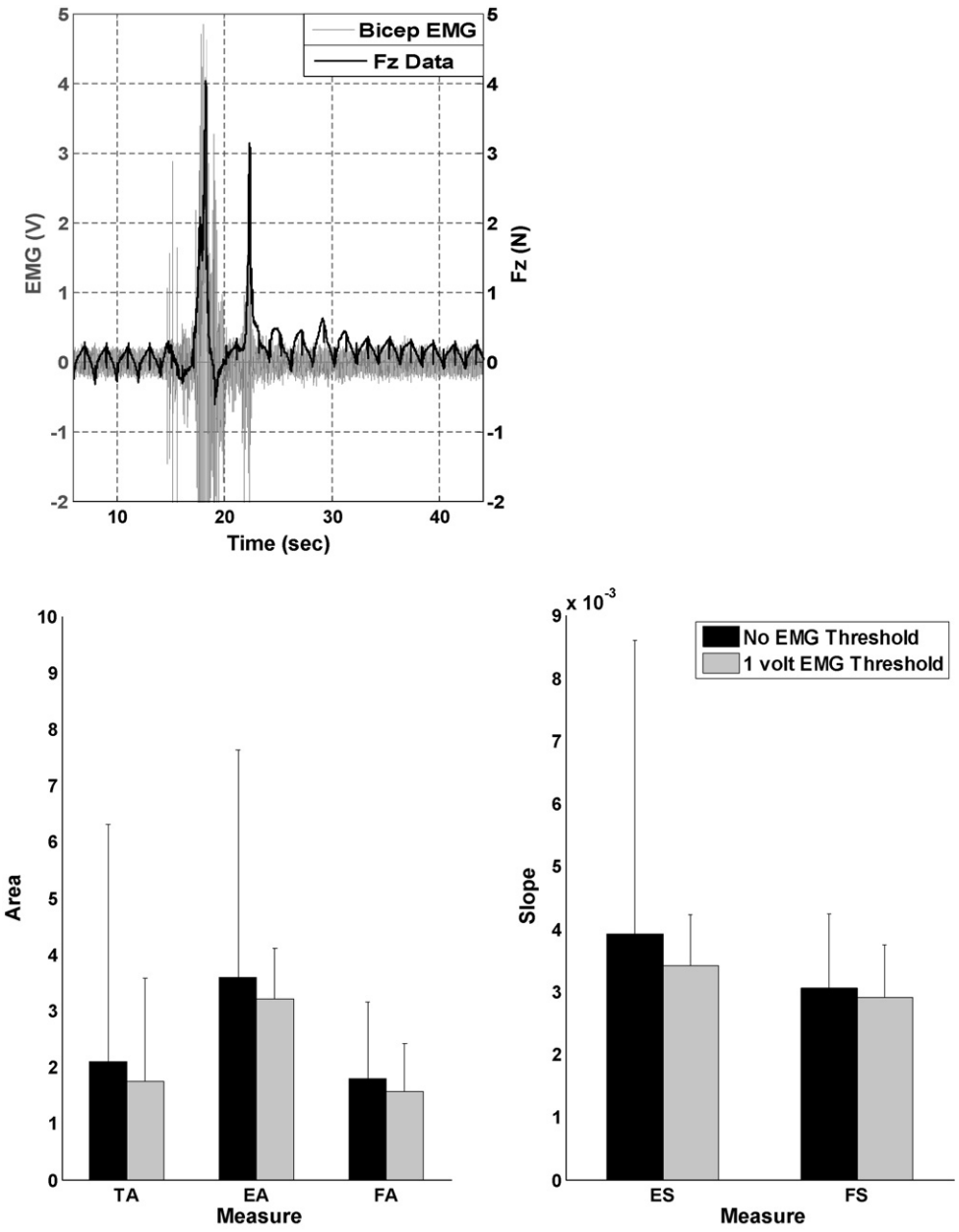

Fig. 5. Bicep and triceps data were recorded during each trial in order to separate active movement/resistance from rigidity. (A) EMG activity correlated well with irregular Fz cycles. (B) Rigidity measure mean and standard deviation differed when comparing a sample Fz data set with and without active resistance removed.

3.4. Changes in rigidity with DBS

The ART system's sensitivity and stability to DBS were evaluated by recording ON- and OFF-STIM. Specifically, these experiments tested (1) the ART system's sensitivity to changes in rigidity measures and (2) whether the same optimal measures for apomorphine apply to DBS. Within a minute of turning the stimulator ON, rigidity measures from monkey 2 exhibited significant improvement (Fig. 8). Comparing OFF-STIM to ON-STIM in this monkey, all five rigidity measures exhibited a significant decrease ($n = 10$, $p < 0.05$) ranging from 25% for FA to 70% for FS. Fig. 8A shows a reduction in the loading and unloading hysteresis plot represented by the decreased shaded area and flattening effect of the extension and flexion curves. In contrast, rigidity measures of monkey 3 exhibited no significant change ($n = 10$, $p > 0.95$), except for EA (Fig. 9).

4. Discussion

In this study, an objective and quantitative technique to characterize the severity of Parkinsonian rigidity in MPTP-treated monkeys was developed and tested. The ART system rotated the primate's arm between two specified angles at constant speed and recorded physiological resistance to the movement through multi-directional force transducers. The procedure was designed to replicate standard examination procedures for measuring upper extremity rigidity. Rigidity outcome measures from the ART system were examined following i.m. apomorphine injection and GPi-DBS therapy, two therapeutic techniques known to reduce Parkinsonian rigidity.

Rigidity is characterized by an increase in muscle tone during the resting state and mediated by peripheral feedback (McAuley, 2003). Accurate assessment of rigidity requires identification of

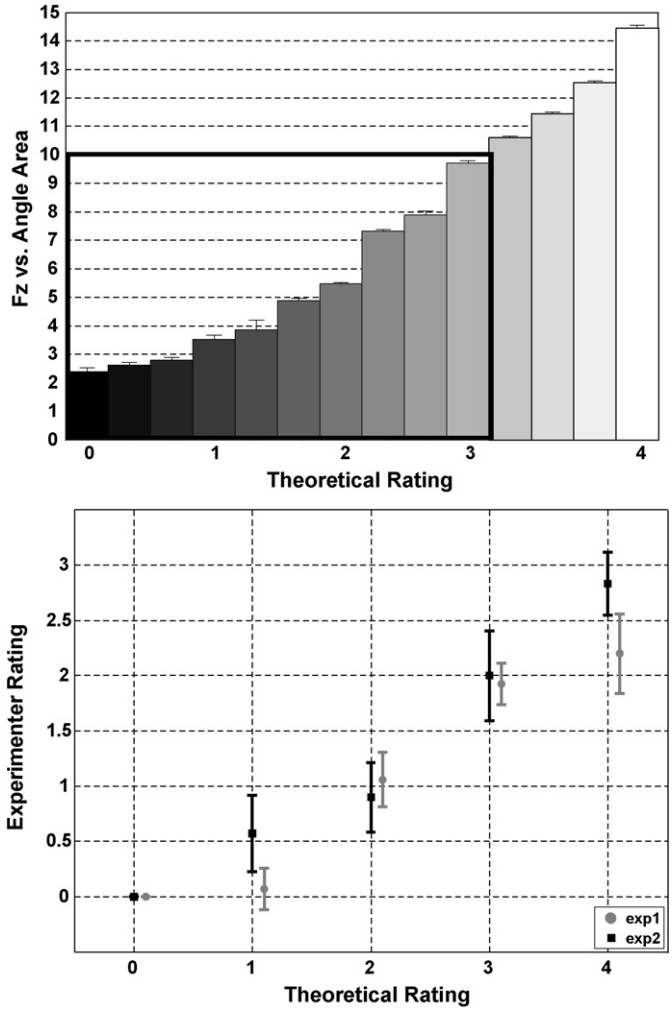

Fig. 6. A mock arm was developed as a controlled system for fine adjustments of rigidity. (A) The mock arm was attached to the ART system, and the rigidity measure total area (TA) was calculated for small changes in rigidity. The black box highlights the TA range appropriate for primate rigidity based on our studies. (B) Two primate specialists evaluated mock arm rigidity settings (0–4) in a blind random study.

active resistance. This is especially relevant given the inability to consistently obtain cooperation from monkeys during manual assessment. Active resistance may impact clinical estimation of rigidity; thus, potentially making current methods imprecise. Incorporating the collection of EMG data into the assessment, while not new to human PD rigidity assessments (Caligiuri, 1994; Patrick et al., 2001; Xia et al., 2006; Xia and Rymer, 2004), provided a means to monitor active resistance in the non-human primate model. Fig. 5B indicates a significant reduction in rigidity measure variance when EMG methods were implemented.

The ART system has several advantages over clinical evaluations when assessing rigidity in non-human primates. First, the system removed the inherent bias of clinical scoring by keeping assessment parameters constant: arm range of motion, extension/flexion velocity, rotation range, and shoulder posturing. Fig. 2B indicates that velocity remained constant throughout extension and flexion; however, this was not the case with the human evaluators who moved the mock arm at an average of 37 ± 29 mm/s. In order to detect small changes in rigidity, velocity must remain constant during the analyzed portions of extension and flexion cycles to prevent the introduction of acceleration forces. Second, the ART system enabled repeated evaluations without having to bring in multiple raters to attain statistical significance, which eliminated concerns due to inter-rater reliability. Third, the system was able to continuously monitor the progression of rigidity over time. This provided a means to examine therapeutic onset latencies as well as the amount of time a particular 'dose' remained effective. Continuous manual arm manipulation in primates, though possible for the experimenter, is not practical and potentially less accurate in detecting small changes in rigidity.

The importance of a baseline rigidity measure cannot be overlooked. The experimenter will typically establish a baseline level prior to systemic MPTP injection by manually manipulating the primate's arm. However, future clinical assessments of rigidity may be relative to this perceived value, which is likely to drift over time. With an intracarotid injection of MPTP, a comparison may be performed between the non-affected and affected limb in which the non-affected limb serves as a baseline. In either case, the experimenter must recall the level of rigidity prior to MPTP injection or compare separate arms. Both methods are highly subjective and depend on rater's level of experience. The baseline established by the ART system, on the other hand, is not influenced by the limitations of current human clinical rating systems.

Similar quantitative systems for characterizing rigidity of the elbow, wrist, and trunk have been developed for human subjects with PD (Caligiuri, 1994; Mak et al., 2007; Prochazka et al., 1997; Sepehri et al., 2007; Xia et al., 2006; Xia and Rymer, 2004), which could potentially be adapted for primates. However, these methods typically used servomotors or manual manipulation to rotate the arm or wrist and record the torque required to overcome passive rigidity (Walshe, 1924; Xia et al., 2006). For the ART system, the primates' arm was directly attached to a force transducer, which is not only sensitive to Fz, but also the *x* and *y* axes and their corresponding torques. These additional force outputs could be utilized for proper elbow positioning or detecting dyskinesia, involuntary and jerky arm movements, attributed to PD medication such as L-Dopa. Another advantage is the ability to conveniently synchronize the ART system with multichannel neurophysiological recording through the LabView software and custom-built controller box.

Five quantitative rigidity measures were selected to characterize the effect of apomorphine injections on rigidity in monkey 1 and categorized into area and slope. Rigidity measures reflected a significant reduction at T1 (~3 min post-injection) and return to baseline levels at T2 (~60 min post-injection). Human studies have reported that effects may last 100 min (Chen and Obering, 2005). ART rigidity measures (ES, FS) returned to ~90% of their baseline at T2 whereas apomorphine extension and flexion area values showed a T2 recovery of 114%, somewhat above the pre-injection value, while FA unexpectedly doubled from pre-injection to T1 (Fig. 7C). The cause of this inconsistency is unknown, but should not invalidate other rigidity measures. When comparing extension and flexion properties separately, our data suggested that slope was more consistent than area. There were no observed differences between extension and flexion slope.

Deep brain stimulation trials consisted of two distinct situations. Monkey 2 showed a statistical decline in ART rigidity measures, confirming therapeutic benefit from previous clinical assessments. Monkey 3 showed no statistically significant drop in rigidity using the ART system. In our primate facility, it has been observed that severity of MPTP-induced motor symptoms may vary among primates. Where rigidity may be the predominant symptom in one subject, another may only present bradykinesia. Previous clinical ratings in this monkey suggest that ON-STIM and OFF-STIM rigidity were moderately significant, decreasing from an average of 1.0 to 0.6. However, clinical assessment of the mock arm shows significant overlap between level 0 and 1 rigidity scores (Fig. 6B). This reaffirms the difficulty with adapting clinical assessment to pri-

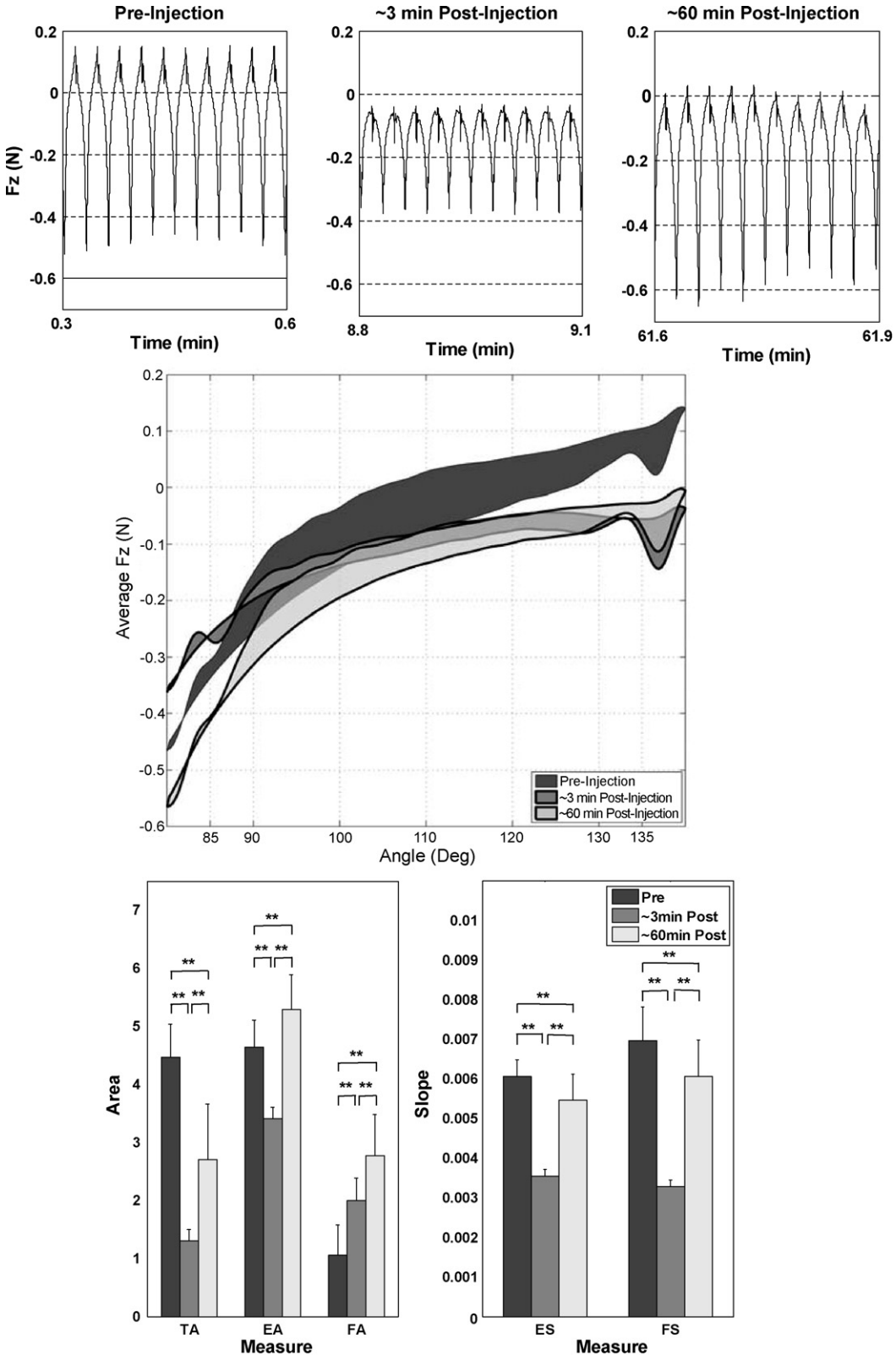

Fig. 7. The ART system detected statistically significant changes in rigidity measures following an intramuscular injection of apomorphine (0.08 mg/kg dose) in monkey 1. (A) Sample filtered Fz waveforms recorded during the pre-injection period, ~3 min post-injection, and ~60 min post-injection. (B) Averaged waveforms showed a reduction in area and slope following injection, which partly recovered after 60 min. (C) Rigidity measures showed differential sensitivity and temporal dynamics. $^{**}p < 0.01$. Error bars denote standard deviation.

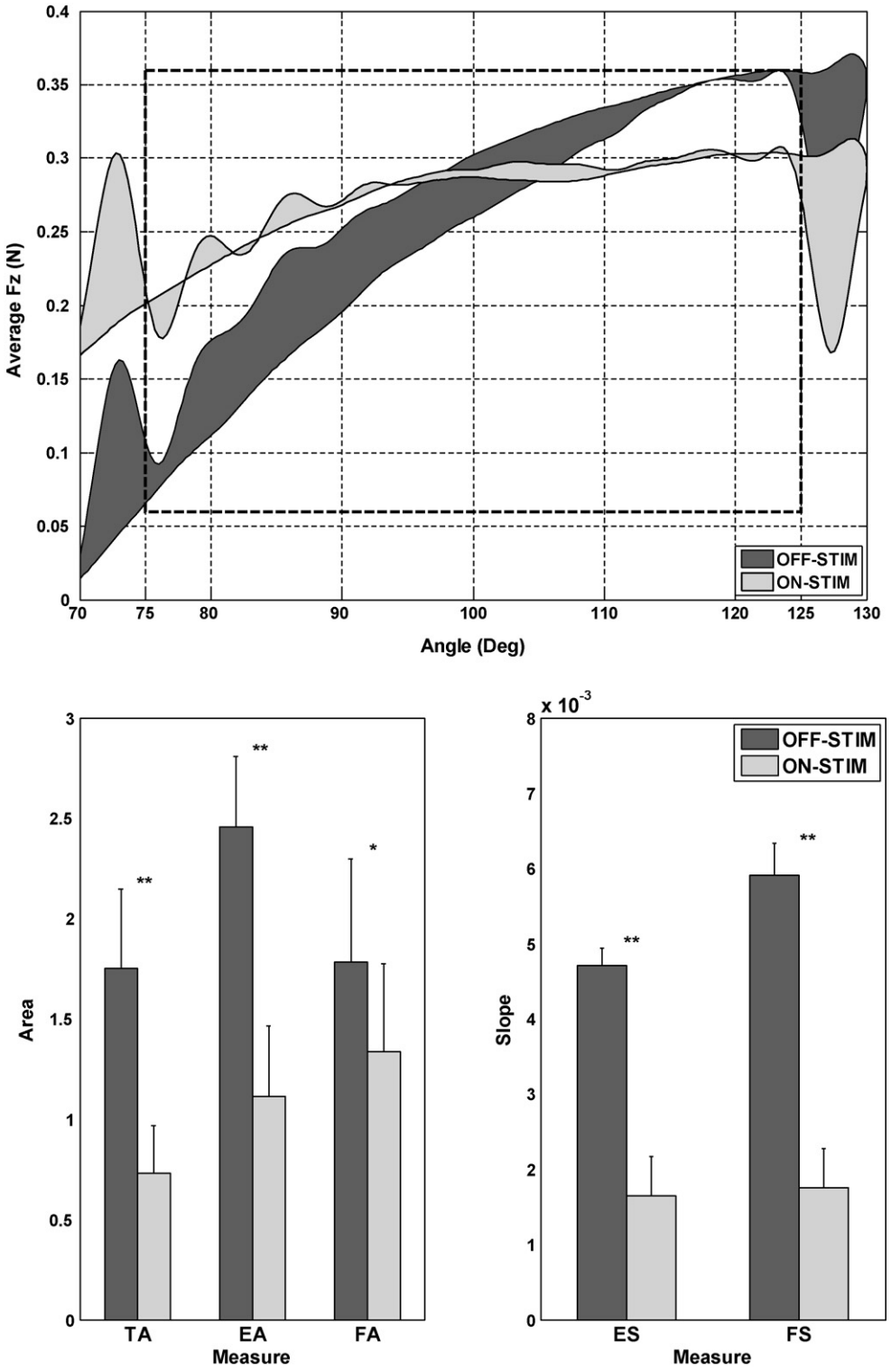

Fig. 8. GPi-DBS produced changes in all rigidity measures as shown for monkey 2. (A) In the DBS-on state, the averaged Fz versus angle plot showed a substantial reduction in area and slope. (B) Across multiple independent rotation cycles, these changes were statistically significant between DBS-off to DBS-on states. $^{*}p < 0.05$, $^{**}p < 0.01$. Error bars denote standard deviation.

mates especially at minimal rigidity and how a more controlled quantitative testing environment is necessary. Integrating the ART system during DBS programming may facilitate improved outcome with less time required for 'optimal' set of stimulation parameters. Additionally, using the ART system concurrent with neural recordings may provide further information on the relationship between neuronal activity and rigidity and the mechanisms underlying the therapeutic effect of DBS to provide an objective and quantitative measure of rigidity. This could help to refine the anatomical site within each stimulation target to minimize rigidity levels.

The ART system is capable of quantifying rigidity in a more controlled and systematic manner than current clinical assess-

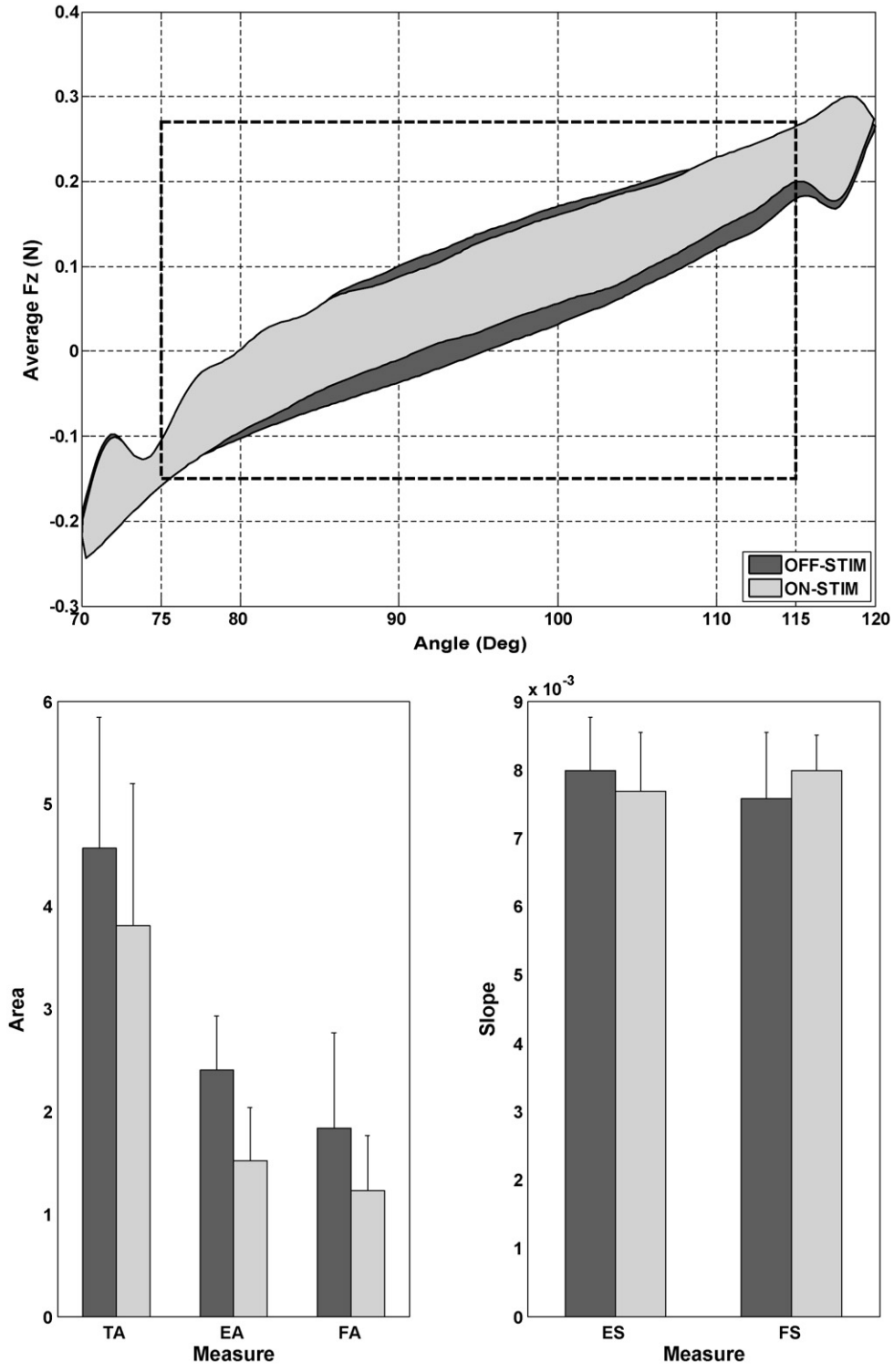

Fig. 9. GPi-DBS did not produce changes in rigidity measures as shown for monkey 3. (A) Averaged Fz versus angle plot showed only a minor reduction in area between DBS-on and -off conditions. (B) Rigidity measures did not show statistical differences between conditions. Error bars denote standard deviation.

ment techniques for primates. This device is unique in that it identifies and eliminates force data affected by active resistance in the monkey. The results of this study suggested that TA, ES, and FS are consistent measures of rigidity, but there was no apparent advantage to analyzing extension and flexion separately. The results from this study are promising, but several improvements should be considered. The ART system is capable of testing either arm; however, the current mounting technique requires further work, specifically preventing the primate elbow from shifting away from the ART axis of rotation. Improvements to the ART system include reducing the overall size of the components to allow for more precise positioning, and allowing the arm to rotate horizontally to eliminate force offset due to arm weight.

The ART system was specifically designed for primate rigidity testing; however, it may be suited for human use as well. Although human subjects are typically more cooperative than primates, monitoring active resistance using EMG recording is still essential, especially for patients with some level of dementia. With telemedicine, the ART system could be adapted for home use where stimulation benefit is assessed by a physician remotely, potentially saving time and money. In addition, a closed system feedback device could be developed to optimize stimulation parameters in real-time directly through the patient's IPG.

Acknowledgements

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