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THE SUPPLEMENTARY MOTOR AREA CONTRIBUTES TO THE TIMING OF THE ANTICIPATORY POSTURAL ADJUSTMENT DURING STEP INITIATION IN PARTICIPANTS WITH AND WITHOUT PARKINSON'S DISEASE

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Abstract—The supplementary motor area (SMA) is thought to contribute to the generation of anticipatory postural adjustments (APAs, which act to stabilize supporting body segments prior to movement), but its precise role remains unclear. In addition, participants with Parkinson's disease (PD) exhibit impaired function of the SMA as well as decreased amplitudes and altered timing of the APA during step initiation, but the contribution of the SMA to these impairments also remains unclear. To determine how the SMA contributes to generating the APA and to the impaired APAs of participants with PD, we examined the voluntary steps of eight participants with PD and eight participants without PD, before and after disrupting the SMA and dorsolateral premotor cortex (dlPMC), in separate sessions, with 1-Hz repetitive transcranial magnetic stimulation (rTMS). Both groups exhibited decreased durations of their APAs after rTMS over the SMA but not over the dlPMC. Peak amplitudes of the APAs were unaffected by rTMS to either site. The symptom severity of the participants with PD positively correlated with the extent that rTMS over the SMA affected the durations of their APAs. The results suggest that the SMA contributes to the timing of the APA and that participants with PD exhibit impaired timing of their APAs, in part, due to progressive dysfunction of circuits associated with the SMA.

Key words: gait, balance, posture, cerebral cortex, transcranial magnetic stimulation.

Patients with Parkinson's disease (PD) are at an increased risk for falls, and they fall most during dynamic transitions in their postural orientation (Bloem et al., 2001). Step initiation represents such a transition, during which patients with PD exhibit freezing, such that they are unable to step and, consequently, often fall (Bloem et al., 2004). Study participants with PD, even those without symptoms of freezing, exhibit diminished, prolonged, and more variable timing of their anticipatory postural adjustments (APAs) before lifting the foot during step initiation (Crenna et al., 1990; Gantchev et al., 1996; Burleigh-Jacobs et al., 1997; Rocchi et al., 2006). The APA represents an important stabilizing feature of step initiation, during which pressure increases under the swing limb to displace and stabilize the center of mass over the stance limb in preparation for the step (Elble et al., 1994). The neural substrates that underlie the impaired APAs of participants with PD, however, are not clear and need to be better understood in order to direct behavioral, pharmacological, and surgical therapies aimed to improve the step initiation of people with PD.

Relatively little is understood about how parkinsonian neuropathology contributes to step initiation, in part, because little detail is available regarding the neural control of step initiation in healthy participants, particularly at the level of the cerebral cortex. The supplementary motor area (SMA), however, represents a potential locus of control for generating the APA as well as a potential locus of neuropathology for the impaired APAs that are evident with PD during step initiation. In general, the SMA contributes to generating self-initiated, multi-segmental voluntary movements (Nachev et al., 2008). With specific regard to gait and step initiation, activation of the SMA is evident using single-photon or positron emission tomography during actual and imagined gait or step initiation (Hanakawa et al., 1999a,b; Malouin et al., 2003). In addition, gait apraxia with ignition failure is evident from individuals with SMA lesions (Della Sala et al., 2002; Nadeau, 2007), but these studies could not detail the specific contribution of the SMA to the generation of the step's APA. Human lesion studies focused on APA function (Gurfinkel and Elner, 1988; Viallet et al., 1992) have shown that loss of the SMA leads to diminished APA amplitudes in preparation for upper limb movements, but these studies did not investigate step initiation, the lesions were often not localized to a single cortical region, and lesion studies are inherently subject to confounding long-term compensatory changes in cortical function (Ward, 2005). Therefore, it remains necessary to determine how the SMA specifically contributes to the generation of the APA during step initiation in order to better understand the neuropathology of impaired step initiation evident with disorders such as PD.

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Abbreviations: APA, anticipatory postural adjustment; CoP, center of pressure; dlPMC, dorsolateral premotor cortex; FDI, first dorsal interosseous; MRI, magnetic resonance image; PD, Parkinson's disease; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; SMA, supplementary motor area; TA, tibialis anterior; UPDRS, unified Parkinson's disease rating scale.

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In addition to the studies implicating the SMA in the generation of the APA, people with PD exhibit altered SMA function when stepping. Specifically, people with PD exhibit hypoactivity of the SMA during gait (Hanakawa et al., 1999b) and diminished pre-movement electroencephalographic potentials during step initiation (Vidailhet et al., 1993), which are thought to represent SMA activation that contributes to the generation of APAs (Saitou et al., 1996). Therefore, impaired APAs appear coincidental with impaired SMA activity during stepping for people with PD, although changes in SMA activity have never been directly associated with changes in the characteristics of the APA during step initiation.

In order to provide a more detailed understanding of how the SMA contributes to the generation of the APA in people with and without PD, it would be useful to elicit a temporary disruption of the SMA and to record individuals with and without PD as they initiate steps during this period of disrupted SMA function. To do so, we selectively disrupted the SMA with sub-threshold, 1-Hz repetitive transcranial magnetic stimulation (rTMS) and evaluated the effects of the stimulation on the APA during step initiation. We also applied rTMS over the dorsolateral premotor cortex (dlPMC) as a control site because it is not hypothesized to be involved in the control of APAs during self-initiated movement. To our knowledge, this is the first study to utilize rTMS over the SMA for the purpose of studying the APA during step initiation, as previous TMS studies evaluating the role of the cerebral cortex during dynamic postural tasks assessed the motor evoked potentials elicited by TMS to the primary motor cortex during step initiation (MacKinnon et al., 2007), an upper-limb unloading task (Kazennikov et al., 2008), steady-state gait (Schubert et al., 1997), or postural responses to an induced loss of balance (Taube et al., 2006).

Consistent with lesion studies (Gurfinkel and Elner, 1988; Viallet et al., 1992), we hypothesized that the SMA contributes to generating the amplitude and timing of the APA. Because decreased APA amplitudes and increased latencies appear to coincide with decreased SMA activity, we predicted that a temporary inhibition of the SMA by sub-threshold, 1-Hz rTMS (Touge et al., 2001) would decrease APA amplitudes and increase APA durations. We also hypothesized that participants with PD exhibit impaired step initiation due to dysfunction of the SMA. We thus predicted that rTMS over the SMA would alter the APAs of participants with PD such that the extent of these stimulation-induced changes would relate to the severity of their motor symptoms because increasing motor impairment would associate with escalating SMA dysfunction, thereby increasing susceptibility to rTMS.

EXPERIMENTAL PROCEDURES

Participants

Eight individuals with idiopathic PD (Hughes et al., 1992) and eight individuals without PD participated in the protocol after providing written informed consent in accordance with the Helsinki agreement. The local Institutional Review Board approved the protocol. Each group consisted of seven males and one female. Participants were chosen to ensure similar characteristics. Consequently, no significant differences were evident between the groups with and without PD, respectively, in mean (±SD, standard deviation) age (62±11 versus 64±10 years), height (176±6 versus 174±11 cm), and weight (74±10 versus 81±9 kg) (respectively, $T=0.34$, 0.37, and 1.58; $P=0.74$, 0.72, and 0.14).

All participants with PD were tested while in the practical "off" medication state, at least 12 h after their last dose of anti-Parkinson's medication. Participants with other neurological, muscular, or psychiatric disorders (e.g., diabetes, peripheral neuropathies, uncorrected visual problems, hearing problems, joint pain, arthritis, fracture, stroke, seizure, migraine, or frequent severe headaches) were excluded. Participants with surgical implants, significant postural tremor, dyskinesia, or dementia were also excluded. Prior to each experiment, a neurologist trained in movement disorders evaluated the severity of the PD participants' motor symptoms using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr scale (Hoehn and Yahr, 1967; Fahn and Elton, 1987). Total scores ranged from nine to 28 on the motor examination of the UPDRS and from two to three on the Hoehn and Yahr scale. Based on these evaluations, all participants with PD exhibited mild to moderate PD with limb rigidity, impaired gait, and bradykinesia.

Stepping protocol

The task was for the participants to stand with each foot on a force plate and then to take two self-initiated, forward voluntary steps with their eyes closed. The participants were asked to step without cues and with their eyes closed because participants with PD preferentially activate the dlPMC (Hanakawa et al., 1999a; Cunnington et al., 2001) as well as increase APA amplitude, step length, and step velocity toward healthy values when provided with sensory cues (Burleigh-Jacobs et al., 1997; Lewis et al., 2000; Morris et al., 1996, 2005; Suteerawattananon et al., 2004).

The participants stood in a stance width that equaled 11% of their body height as measured from the center of one heel to the center of the other (McIlroy and Maki, 1997). The perimeters of the participants' feet were marked with tape to ensure that stance width remained consistent throughout the experiment. We monitored the force distribution under the participants' feet by an oscilloscope to ensure that the participants stood with an equal amount of weight under each foot prior to stepping. To prevent the participants from falling, they were harnessed to a ceiling-mounted track that did not provide any support during the task unless they began to fall.

The participants were instructed to close their eyes and, after a self-selected amount of time, to step forward with a pre-determined stepping foot, followed by a matching step with the initial stance limb to bring their feet back to parallel. The participants with PD were instructed to step with the leg most affected by the disease, as determined from the UPDRS motor examination, and those without PD stepped with the same leg as the participant with PD who was most closely matched for gender and age. Each participant performed nine steps before rTMS and nine steps after rTMS. The participants performed separate sessions in counterbalanced order for rTMS over the SMA and dlPMC. The sessions were separated by at least 7 days, and the participants with PD always performed the experiment in the morning, after withholding their anti-Parkinson's medications overnight.

As part of a larger protocol, the participants also performed visually cued voluntary steps, forced steps in response to platform translations, and quiet stance trials with their eyes closed. The tasks were ordered such that the participants first performed three trials of self-initiated steps, followed by three-trial blocks of the other tasks (Table 1). This sequence was repeated twice more to achieve a total of nine trials for each task. The first three self-initiated steps were, therefore, always ordered before the other tasks and, because the significant effects of rTMS were only

Table 1. Presentation of the self-initiated step condition within the larger protocol

Trials	Condition			
	Self-initiated stepping	Cued stepping	Forced stepping	30 s quiet stance
1–3	X			
4–6		X		
7–9			X	
10				X
11–13	X			
14–16		X		
17–19			X	
20				X
21–23	X			
24–26		X		
27–29			X	
30				X
30 min rTMS				
31–33	X			
34–36		X		
37–39			X	
40				X
41–43	X			
44–46		X		
47–49			X	
50				X
51–53	X			
54–56		X		
57–59			X	
60				X

evident for one trial after stimulation, the analyses for this study pertain only to the self-initiated steps with the eyes closed.

rTMS protocol

After completing the stepping protocol, the participants sat upright in an adjustable dental chair mounted on locking wheels to prepare them for rTMS. For each participant, we first marked the scalp with a 1-cm grid of lines centered at the scalp's vertex (according to the 10/20 system; Jasper, 1958) using a wax pencil. We defined the SMA and dlPMC locations of rTMS as a specified distance from the optimal positions to stimulate the tibialis anterior (TA, a distal leg muscle) and the first dorsal interosseous (FDI, a hand muscle) ipsilateral to each participant's chosen stepping limb using single-pulse stimulations from a Magstim rapid-rate device with a 70-mm, figure-eight, cooled-coil system (Magstim Company Ltd., Whitland, Dyfed, UK). We recorded muscle activity using pre-amplified differential electromyography from silver, silver-chloride electrodes placed over the muscles on the skin's surface. To identify the optimal scalp locations for eliciting motor evoked potentials (MEPs) of maximal amplitude and shortest latency from the FDI and TA muscles (the hotspots), we applied stimulations at multiple locations separated by 1-cm increments, progressing to 0.5-cm increments. For the FDI muscle, the coil was positioned contralateral to the FDI muscle being stimulated and oriented so that its handle pointed approximately 45 ° posterolateral from the mid-sagittal line (Werhahn et al., 1994). For the TA muscle, the coil was oriented so that its handle pointed approximately perpendicular to the mid-sagittal line, ipsilateral to the stimulated TA muscle (Priori et al., 1993; Terao et al., 1994).

After locating the stimulation hotspots for the TA and FDI muscles, we determined the threshold for stimulating the FDI muscle at rest. The rest motor threshold was defined to be the stimulation intensity that elicited MEPs of at least 50 μV in five out of ten consecutive trials of single-pulse stimulations (Rossini et al., 1994). Although the participants performed a stepping task, we determined the rTMS intensities from the rest motor threshold of the FDI muscle because, in our experience, the FDI requires lower stimulation intensity than the TA to evoke muscle activation, and the FDI elicits more stable thresholds than the TA muscle when assessed on separate days. Therefore, using the FDI muscle's threshold, we could produce more consistent stimulation intensities across the experimental sessions (which were separated by at least 7days) and employ lower stimulation intensities that are less likely to induce adverse effects.

After determining the participants' rest motor threshold, we prepared the participants for rTMS by reclining them in the adjustable chair and then fitting an elastic band around their head until the participants felt comfortable while maintaining their head in a stable position (Fig. 1A). For each participant, the intensity of stimulation during rTMS was set to 80% of the FDI's rest motor threshold recorded during that day's session. Repetitive TMS was delivered at 1 Hz for 30 minutes (1800 pulses) through the same stimulator and coil as when locating hotspots and determining motor thresholds. Sub-threshold, 1-Hz stimulations were chosen to maximize the safety of our protocol (Wassermann, 1998) and decrease spread of excitation to adjacent regions (Lang et al., 2006). Every 2.5–5 minutes during rTMS, we monitored the participants to ensure they remained awake and that their head position hadn't shifted. When the 30 minutes of rTMS was complete, we rolled the participants in the chair to the force platform in order to minimize how much they actively moved before repeating the stepping protocol described above, because voluntary contraction can normalize cortical excitability after rTMS conditioning (Touge et al., 2001).

When stimulating the SMA, the coil was positioned 5 cm anterior from the TA muscle's hotspot along the mid-sagittal line. The coil was oriented with its handle pointing posterior along the mid-sagittal line (Cunnington et al., 1996; Obhi et al., 2002; Verwey et al., 2002). These coordinates are consistent with studies using image-guided TMS or functional imaging to localize the pre-SMA/SMA transition (Rushworth et al., 2002; Mayka et al., 2006) so that, when accounting for the caudal extent of the induced electric field from the coil's hotspot (Pascual-Leone et al., 1999), this position likely elicited an induced electric field that spanned the SMA. When stimulating the dlPMC, the coil was positioned 2.5 cm anterior from the FDI muscle's hotspot, with the handle oriented approximately 45 ° posterolateral from the mid-sagittal line (Gerschlager et al., 2001; Chen et al., 2003).

To confirm that our measured scalp locations placed the coil over the intended cortical regions, we obtained an anatomical magnetic resonance image (MRI) of the first healthy participant's brain for use with image-guided TMS. The structural MRI was acquired with a 1.5-tesla magnet using multi-echo, multi-planar acquisition. Images were obtained in the coronal plane at 4-mm thickness. For image-guided TMS, the participant's anatomical MRI was stereotactically co-registered with the participant's head using a Polaris infrared tracking system (Northern Digital, Waterloo, Canada) interfaced with Brainsight software (Rogue Research, Montreal, Canada). The position of the TMS coil was then monitored with respect to the participant's brain, and we acquired digital images of the coil's locations when it was centered over the rTMS and hotspot locations outlined in the methods above.

Data collection and analysis

To capture the participants' APAs, we recorded the lateral displacements of their center of pressure (CoP) from two force plates, one under each of the participants' feet. Each force plate was equipped with four vertical and two horizontal strain gauge transducers. Force signals were amplified and sampled at 480 Hz. Total-body lateral CoP was calculated from the difference in load-

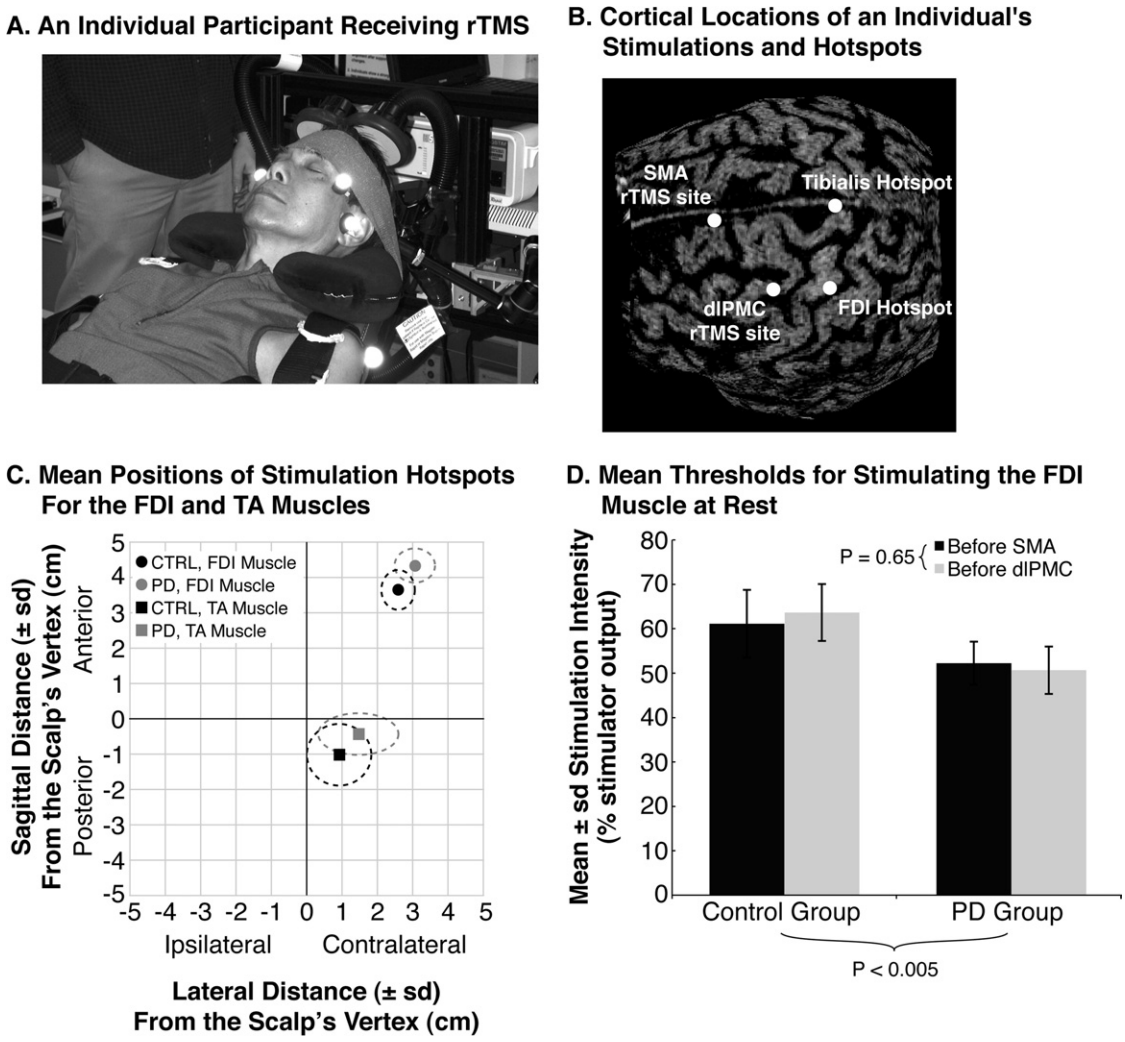

Fig. 1. Characteristics of rTMS. (A) A participant receiving rTMS over the SMA. The participant sat reclined in an adjustable dental chair with a memory foam pillow supporting his head and neck. An elastic band was also wrapped around the forehead to prevent excessive movement. The air-cooled coil of the Magstim rapid device was held in place by an adjustable clamp. (B) Image-guided TMS, demonstrating the cortical locations of muscle hotspots and of rTMS. (C) The average (SD) hotspot locations for the participants with PD (gray symbols and dashed lines) and the participants without PD (black symbols and dashed lines), relative to the vertex of the skull. The squares represent the hotspots for stimulating the TA muscle, and circles represent those for stimulating the FDI muscle. (D) The average (SD) rest motor thresholds of the FDI muscle during the sessions for rTMS over the SMA (dark gray bars) and dlPMC (light gray bars). Repetitive TMS was applied at 80% of each participant's rest motor threshold for that day's session. The *P*-value below the chart represents the main effect of group differences, and the *P*-value next to the inset legend represents the main effect of session differences.

ing of the right and left force plates as previously reported by Henry et al. (1998). Lateral CoP displacements were calculated after subtracting an initial CoP position, which was defined as the average CoP position over the first 500 ms of recording.

The onset of an APA was defined manually with an interactive plotting function programmed in MATLAB software (MathWorks, Inc., Natick, MA, USA). Using this plotting function, we identified the moment when the CoP began to displace toward the swing limb prior to foot-lift. When identifying APA onsets, the CoP plots were unlabeled and randomly ordered to prevent biased identifications. The duration of an APA was calculated as the time when the lateral CoP displacement came back to its initial position just prior to when a participant lifted a foot off the force plate, minus the time when the APA began. Peak APA amplitudes were defined as the maximum lateral displacement of the CoP toward the swing limb just prior to foot-lift.

We calculated each participant's average APA duration, the variability (i.e., the SD) of each participant's APA durations, and the average peak APA amplitude prior to rTMS. Two-factor mixed-model analysis of variance (ANOVA) determined whether these measures were different between groups (with PD versus without PD) and stable between experimental sessions (SMA versus dlPMC). For each site of rTMS, a three-factor mixed-model ANOVA tested for differences in the dependent measures between groups (with PD versus without PD), trials (one through nine), and rTMS (before versus after). The factor for trial was included because it was unclear how long any effects due to rTMS would last. Pearson coefficients were analyzed to determine whether the effects of rTMS on the APAs correlated with the clinical severity of the PD participants' lower-body motor symptoms. Because the results demonstrated that the effects of rTMS lasted for only one trial, the correlations were based on the differ-

ence between a measure's value during the first trial after rTMS and its mean value from the trials before rTMS. The clinical severity of a PD participant's lower-body motor symptoms was defined as the sum of the UPDRS items of leg tremor (sub-scores of item 20) and leg rigidity (sub-scores of item 22), as well as leg agility, arise from chair, posture, gait, postural stability, and body bradykinesia (items 26–31); with a possible range of scores from zero (no symptoms) to 44 (most severe symptoms), this subset of UPDRS items was chosen to render the score more directly relevant to the stepping task (Jacobs and Horak, 2006). Significance was defined as a *P*-value of less than or equal to 0.05.

RESULTS

Locations and intensities of rTMS

The session of image-guided TMS confirmed that our measures located the FDI and TA muscles' hotspots over the pre-central gyrus, and that the locations for rTMS over the SMA and dlPMC were consistent with previous reports localizing these regions (Fig. 1B; Gerschlager et al., 2001; Rushworth et al., 2002). Relative to the vertex of each participant's scalp, the sagittal position of the FDI muscle's hotspot was more anterior for the participants with PD than for the participants without PD (main effect of group: $F=7.54$, $P<0.05$) (Fig. 1C). The sagittal position of the TA muscle's hotspot and the lateral positions of the TA and FDI muscles' hotspots were not significantly different between the participants with and without PD (main effect of group: $F=1.13–2.94$, $P=0.11–0.31$). Rest motor thresholds were significantly lower in the participants with PD compared to those without PD (main effect of group: $F=14.06$, $P<0.005$), but thresholds remained similar between experimental sessions (main effect of session: $F=0.22$, $P=0.65$) (Fig. 1D). Based on timestamps associated with the electronic files for each trial, the first two stepping trials were initiated within two minutes after rTMS for both participant groups.

APA characteristics before stimulation

The participants with PD exhibited impaired APA control. Specifically, although APA durations were, on average, similar between participants with and without PD (main effect of group: $F=1.71$, $P=0.21$), APA durations were more variable for the participants with PD (main effect of group: $F=5.45$, $P<0.05$) (Fig. 2A, B). The participants with PD also exhibited smaller peak APA amplitudes than the participants without PD (main effect of group: $F=12.82$, $P<0.005$) (Fig. 2C). No significant differences were evident between the experimental sessions for any measure of the APA (main effects of session: $F=0.02–0.99$, $P=0.34–0.88$) (Fig. 2).

Effects of rTMS

APA durations significantly decreased for the first stepping trial after rTMS over the SMA (interaction effects of rTMS and trial: $F=2.25$, $P<0.05$), whereas APA durations remained similar after rTMS over the dlPMC (interaction effects of rTMS and trial: $F=1.26$, $P<0.27$) (Fig. 3A, B). No significant (two) or three-way interactions were evident among the factor for group and the factors for trial and

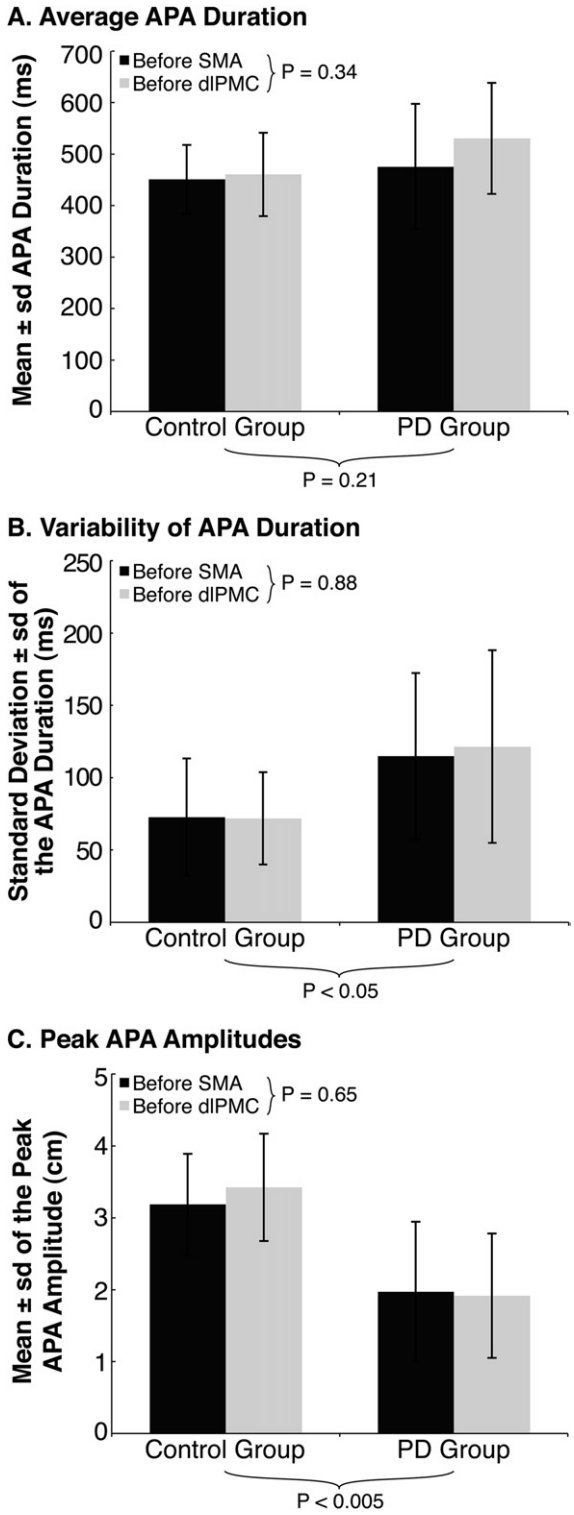

Fig. 2. Characteristics of the APA prior to rTMS. The charts illustrate each group's average (SD) (A) APA duration, (B) inter-trial variability of APA duration, and (C) peak APA amplitude prior to rTMS during the SMA (dark gray bars) and dlPMC (light gray bars) sessions. *P*-values below the charts represent main effects for group differences, those next to the inset legends represent main effects for session differences.

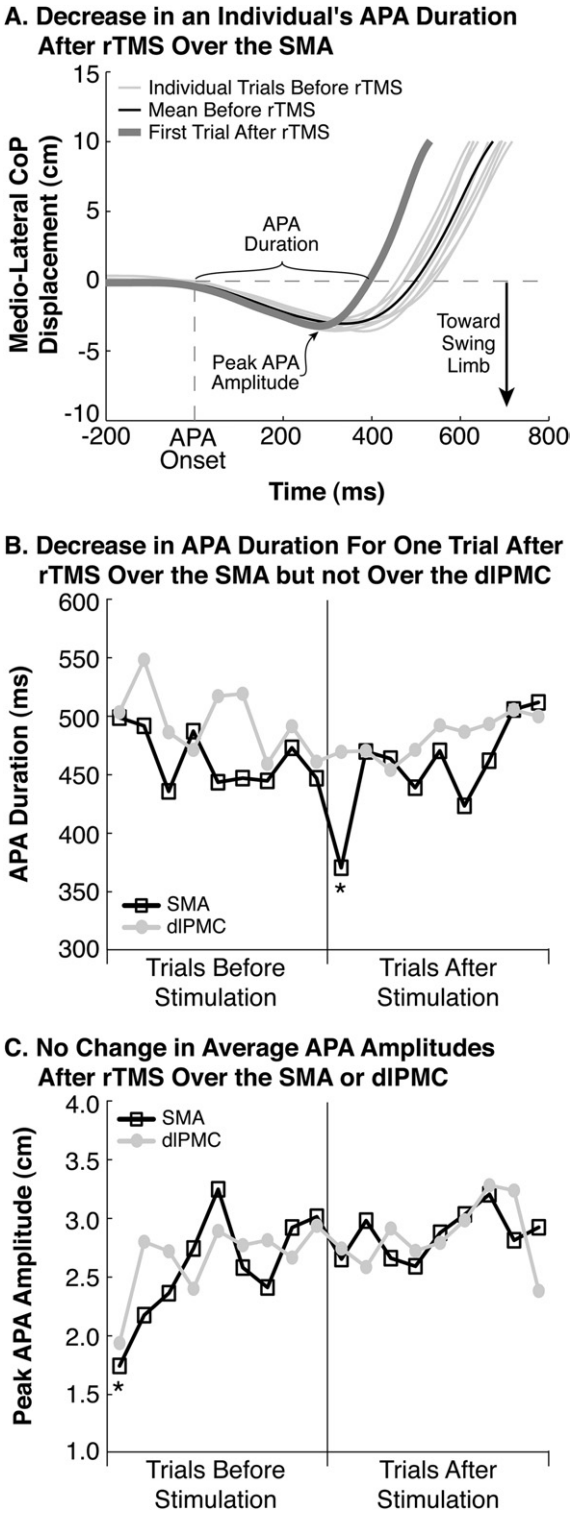

Fig. 3. Effects of rTMS on the APA. (A) An example of shortened APA duration for one trial after rTMS over the SMA from an individual with PD. The horizontal axis represents time relative to APA onset, and the vertical axis represents the lateral displacement of the CoP for individual trials before stimulation (the thin gray curves), the average of trials before stimulation (the thin black curve), and for the first trial after SMA stimulation (the thick gray curve). Negative displacements are directed toward the participant's swing limb. (B) Average APA durations by trial for all participants, demonstrating how APA durations decreased for only one trial after SMA stimulation; no group effects were evident. The black line with squares represents the mean APA durations from the session of rTMS over the SMA; the gray line with circles, the session of rTMS over the dlPMC. The asterisk highlights the first trial after rTMS because this trial was significantly different from others. (C) Average peak APA amplitudes by trial for all participants, demonstrating how APA amplitudes were smallest for the sessions' first trials compared to subsequent trials (asterisk); no significant changes following rTMS and no group effects were evident.

rTMS, either for rTMS over the SMA or the dlPMC (range of $F=0.09–1.46$, range of $P=0.18–0.77$). The lack of significant interactions involving group differences appears due to high inter-individual variability within the group with PD: the mean ($\pm$SD) decrease in APA durations between the first trial after rTMS over the SMA and the mean of trials before rTMS was 130 ± 113 ms for the group with PD compared to 55 ± 18 ms for the group without PD.

Stimulation with rTMS over the SMA or dlPMC had no effect on APA amplitudes. Although significant differences in peak APA amplitudes were evident among trials (main effect of trial: $F=2.88$, $P<0.01$), with interactions among the trials before and after rTMS over the SMA (interaction effects of rTMS and trial: $F=2.67$, $P=0.01$), these effects were not related to the rTMS but were evident due to smaller peak APA amplitudes during the first trial of the session relative to subsequent trials (Fig. 3C). Although not statistically significant, similar trends were evident during the dlPMC session (Fig. 3C) (main effect of trial: $F=1.78$, $P=0.09$; interaction effects of rTMS and trial: $F=1.59$, $P=0.16$). No significant two or three-way interactions were evident among the factor for group and the factors for trial and rTMS, either for rTMS over the SMA or the dlPMC (range of $F=0.29–0.53$, range of $P=0.60–0.83$).

The effect of rTMS over the SMA on the APA durations of the participants with PD significantly correlated with the severity of their lower-body symptoms (Pearson $r^2=0.70$, $P<0.01$) (Fig. 4).

DISCUSSION

The results demonstrated that rTMS over the SMA transiently shortened APA durations, whereas rTMS over the dlPMC did not, and no effects of rTMS were evident on APA amplitudes. In addition, the extent to which rTMS over the SMA affected the APA durations of the participants with PD positively correlated with the clinical severity of their lower-body motor symptoms. While rTMS over the SMA consistently decreased APA durations by less than 100 ms for the participants without PD, rTMS elicited far greater decreases in APA duration for the participants with PD who exhibited the greatest symptom severity. It has been suggested that the progression to the late stages of PD associates with a progressive degeneration of cortical structures such as the SMA (Braak et al., 2002). Therefore, we speculate that the increased efficacy of rTMS to alter the APA durations of participants with more severe parkinsonian symptoms likely reflects greater susceptibility of the

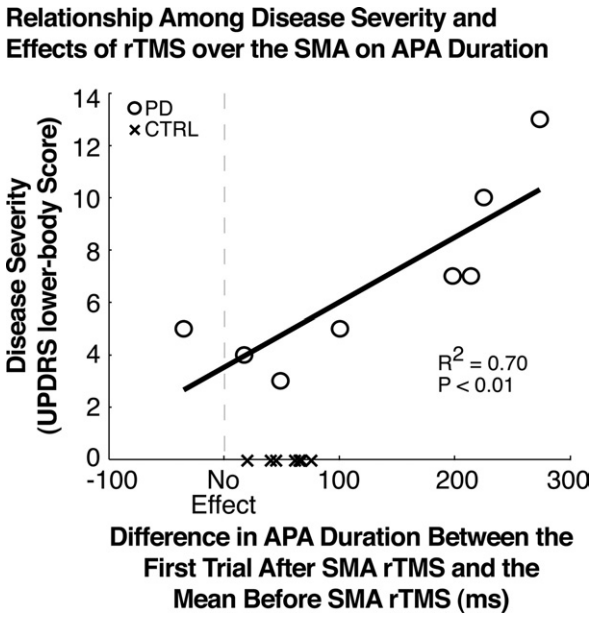

Fig. 4. A scatter plot illustrating a significant correlation among the PD participants' disease severity (measured by lower-body motor UPDRS scores) and the extent that rTMS over the SMA affected APA durations. The circles represent the values for individual participants with PD; the Xs, those of the participants without PD. Although the UPDRS was not assessed for those without PD, their values are depicted with an assumed UPDRS score of zero. The horizontal axis has been changed so that positive values represent a decrease in APA duration following rTMS in order to illustrate a positive correlation among disease severity and the effect of rTMS on APA duration.

SMA to rTMS due to its progressive degeneration. Any further speculation regarding the cellular basis of this effect is precluded, however, by a lack of understanding for whether sub-threshold, 1-Hz rTMS over the SMA elicits the same decrease in corticospinal excitability and the same dysfacilitation of corticocortical excitability as that which results from similar stimulations of the primary motor cortex (Romero et al., 2002). Further, it remains unclear whether the effects of rTMS over the SMA on APA durations result from alterations in corticospinal activity or in extra-pyramidal activity. Therefore, further study is necessary to identify the neurophysiologic basis by which rTMS over the SMA affects the APA during step initiation. Nevertheless, the specificity of the effects to only the SMA confirms that the effects were due to the stimulation of that cortical location and not due to trial order or the general procedures experienced during both rTMS sessions (such as lying reclined during stimulation). Taken together, then, the results suggest that the SMA contributes to coordinating the timing of the APA, and participants with PD exhibit impaired step initiation, in part, due to progressive dysfunction of circuits involving the SMA.

The direction and length of time with which rTMS effected APA durations, however, were contrary to our predictions: rTMS over the SMA shortened APA duration without altering APA amplitude, suggesting an increase in the velocity of the APA's weight shift, and the effect of rTMS lasted for only one trial after stimulation. Regarding the duration of the effect, it has been reported that voluntary muscle activation can normalize rTMS-induced changes in cortical excitability (Touge et al., 2001). Thus, in our study, any rTMS-induced changes in the participants' neuromotor state may have been normalized after the first trial due to feedback processing experienced during the first trial after stimulation. Regarding the direction of the rTMS effect on APA durations, our assumption of decreased SMA activity may be false: in a study investigating brain activation during sequential hand movements, participants with PD were reported to exhibit decreased activation of the rostral SMA but increased activation of the caudal SMA (Sabatini et al., 2000). Thus, the decrease in APA duration observed in this study may reflect either a more significant effect of rTMS to the caudal SMA than to the rostral SMA, or an inhibitory role of the SMA in defining the duration of the APA, such that activation of the SMA slows the APA.

The lack of effect of rTMS on APA amplitudes was also contrary to our predictions based on previous reports of diminished APA amplitudes with lesions to the SMA (Gurfinkel and Elner, 1988; Viallet et al., 1992). The decrease in APA amplitude with cortical lesions, however, may reflect a lack of regional specificity of the lesions or reflect effects of the lesions on other regions with input from the SMA that are also hypothesized to contribute to generating the APA, such as the primary motor cortex or the basal ganglia (Massion, 1992; MacKinnon et al., 2007). Thus, the SMA may contribute to the timing of the APA, whereas amplitude modulation may be relegated to the primary motor cortex or basal ganglia.

The effects of rTMS to a specific region of the cerebral cortex, however, may not represent a direct effect of that cortical region on the behavior. Studies have demonstrated that sub-threshold, 1-Hz rTMS over one site can elicit changes in the activity and excitability of other neural sites, presumably through communicating fibers (Gerschlager et al., 2001; Speer et al., 2003; Bestmann et al., 2005). Thus, in this study, changes in APA duration after rTMS over the SMA may represent an indirect influence of the stimulated site on other neural centers involved in regulating postural preparation during step initiation. We suggest, however, that the SMA likely exerts some direct influence because (1) no significant changes in APA duration were evident following rTMS over the dlPMC, which (like the SMA) represents an executive motor center with projections to the primary motor cortex and to the motor horn of the spinal cord (Dum and Strick, 2002), and (2) the effects of rTMS over the SMA on APA duration were evident in both the groups with and without PD, suggesting this effect was not indirectly related to the differential projections of the SMA and dlPMC to the basal ganglia (Leh et al., 2007).

Consistent with previous reports (Tremblay and Tremblay, 2002; Lou et al., 2003), the motor thresholds for stimulating the FDI muscle were lower for the participants with PD than for those without PD. Consequently, rTMS intensities were lower for the participants with PD and stimulating the groups with different absolute intensities may have diminished the effect of rTMS on the participants with PD. The intensities, however, were normalized to the

cortico-spinal excitability of each participant, and our results never showed any group-by-stimulation interactions characterized by an effect of rTMS in the group without PD and no effect in the group with PD. In addition to decreased motor thresholds, hotspot locations were displaced for the participants with PD compared to those without PD, which is consistent with an altered somatotopic organization of the primary motor cortex in people with PD. Such a shift has been previously reported and postulated to be evident due to a shift in the synaptic excitability of inputs to the primary motor cortex consequent to the altered excitability of the striato-thalamo-cortical loops that occurs with PD (Thickbroom et al., 2006).

CONCLUSION

In summary, the results support a neural control model for voluntary step initiation in which the SMA coordinates the timing of the APA, independent of control on APA amplitude. In addition, patients with PD likely exhibit abnormal APA timing due to dysfunction of the SMA, whereas diminished APA amplitudes may be a result of pathology to other affected regions such as the primary motor cortex or the basal ganglia. The results suggest that the impaired balance and mobility of individuals with PD may be associated with dysfunction of the SMA and that treatments targeted to improve this dysfunction may be useful to ameliorate the disabilities associated with impaired step initiation.

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