Postural Preparation Prior to Stepping in Patients with Parkinson’s Disease

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ABSTRACT

People with Parkinson's disease (PD) frequently have difficulties with generating anticipatory postural adjustments (APAs) for forward propulsion and lateral weight transfer when initiating gait. This impairment has been attributed to deficits in motor planning and preparation. This study examined the preparation of APAs prior to an imperative cue to initiate forward stepping. A startling acoustic stimulus (SAS) was used to probe the state of preparation of the APA in 8 PD (off medication) and 7 matched Control subjects. Subjects performed visually cued trials involving a pre-cue light instructing them to prepare to step, followed 3.5 seconds later by a go-cue light to rapidly initiate stepping. In random trials, a SAS (124 dB) was presented at -1500, -1000, -500, -250, -100, or 0 ms before the go-cue. Subjects also performed self-initiated steps. Ground reaction forces (GRFs), center of pressure (CoP) changes, and electromyographic (EMG) signals were recorded. The SAS triggered APAs in 94 ± 11% (PD) and 96 ± 8% (Controls) of trials at latencies 89 ± 4 ms (PD) and 97 ± 3 ms (Controls) earlier than Control trials. The temporal profile of APA preparation was similar between groups. However, peak EMG, GRF, and medio-lateral CoP amplitudes were reduced in PD. SAS-evoked APAs at 0 ms matched Control trial APAs and were enhanced compared with self-initiated stepping. These results demonstrate that people with mild to moderate PD can plan and prepare the appropriate APA sequence prior to the expected cue to initiate gait, however, the prepared APAs are underscaled in magnitude.

Keywords: Parkinson’s disease; motor preparation; posture; gait initiation; akinesia
Introduction

In patients with Parkinson’s disease (PD), an extensive array of motor control deficits in posture, balance, and gait performance has been identified (Martin, 1967, Rogers, 1996, Morris et al., 2001, Grimbergen et al., 2004; Boonstra et al., 2008). In particular, difficulty with initiating stepping or gait, often referred to as ‘start hesitation’, is a commonly observed impairment. In healthy individuals, gait initiation is characterized by an anticipatory postural adjustment (APA) phase that precedes and accompanies the initiation of the stepping phase (Carlsoo, 1966, Mann et al., 1979, Brunt et al., 1991, Crenna and Frigo, 1991). For forward stepping, APAs involve a sequence of muscle activations and changes in the ground reaction forces that move the net center of pressure (CoP) beneath the feet backward and toward the initial swing limb (Carlsoo, 1966, Breniere and Do, 1986, MacKinnon et al., 2007). This motor sequence produces the forces and moments necessary to propel the body center of mass (CoM) forward in the intended direction of stepping and laterally towards the single stance limb prior to the onset of the first step. Compared with healthy individuals, the ground forces characterizing early APAs in PD are often abnormally prolonged in duration and reduced in amplitude with a delay in the onset timing of stepping (Crenna and Frigo, 1990, Gantchev et al., 1996, Burleigh-Jacobs et al., 1997, Vaugoyeau et al., 2003, Mille et al., 2007; Rogers et al., 2011). This delay may include abnormal pauses in muscle activation patterns that disrupt the posture-movement sequence (Crenna and Frigo, 1991). Moreover, while APAs are normally almost always present during voluntary stepping, they may often be absent in PD patients (Crenna et al., 1991, Burleigh-Jacobs et al., 1997). Thus, the normal spatial and temporal sequencing between the APA and stepping components of gait initiation is disrupted (Rogers et al., 2011).
It has been hypothesized that deficits in the initiation of voluntary movement in people with PD are mediated by abnormalities in the preparation of the planned action (Berardelli et al., 2001). Impaired preparation is reflected in increased simple reaction times (Pullman et al., 1988, Jahanshahi et al., 1992) and a significant attenuation of the early phase of movement-related cortical potentials that precede both self-paced (Dick et al., 1989, Dick et al., 1989, Cunnington et al., 1995, Jahanshahi et al., 1995) and cued upper limb movements (Cunnington et al., 1995). A similar attenuation of preparatory cortical activity has been shown prior to gait initiation (Vidalhlet et al., 1993), yet paradoxically, no reduction in movement-related potentials was observed in a cohort of patients with start hesitation (Vidalhlet et al., 1995). Moreover, it has been shown that impairments in the initiation of gait in the off-medication state can be overcome with the provision of externals cues (Burleigh-Jacobs et al., 1997), even in those with profound akinesia and freezing of gait (Glickstein and Stein, 1991). Currently, the mechanisms by which external cues mediate the improvements in the release of the gait initiation sequences are poorly understood.

It has recently been shown that the state of preparation of an intended action can be probed using a startling acoustic stimulus (SAS). Valls-Solé et al. (1999) were the first to show that coordinated movement sequences, including those involving APAs, could be triggered when an imperative reaction time (RT) cue is replaced by a SAS. Moreover, the movement sequence is initiated with RTs considerably shorter than a normal simple voluntary reaction, yet the spatial and temporal features of the intended movement are unaltered. Based on reaction time arguments, it was proposed that the prepared motor program triggered by the loud SAS is released from the same reticular brainstem structures that mediate the startle reflex rather than by motor cortical pathways (Valls-Sole et al., 1999). It was subsequently shown that the rapid
release of the sequence only occurred under simple reaction time conditions (Carlsen et al., 2004), suggesting that advance preparation of the intended action was a prerequisite for movement release. Using a delayed-instruction paradigm, we have shown that, in healthy young adults, the presentation of SAS up to 1400 ms prior to the imperative cue to initiate forward stepping often resulted in the rapid release of the APA sequence (MacKinnon et al., 2007). These findings provided evidence that APAs are progressively prepared well in advance of step initiation in healthy subjects and that a SAS can be used to probe the state of preparation of the motor system. Accordingly, the purpose of this study was to use the SAS paradigm to investigate whether deficits in step initiation in patients with mild to moderate idiopathic PD are associated with impaired preparation and planning of APAs prior to forward stepping. We hypothesized that: (1) preparation of the APA sequence would be significantly impaired in the subjects with PD compared to matched Control subjects, as evidenced by a reduced incidence and attenuated magnitude of the appropriate APA sequence evoked by a SAS, particularly during the early phase of movement preparation and (2) that significant differences between groups in the timing and magnitude of the APAs preceding self-initiated steps would be ameliorated by the presentation of a simple visual cue or presentation of a SAS at 0 ms.

Methods

Subjects

Fifteen community dwelling adults participated in this study; eight patients with PD (see Patient Characteristics in Table 1) and seven healthy matched control subjects (4 male, 3 female, mean age = 65.6 years ± 7.6 SD). Individuals with PD were recruited from the Parkinson’s Disease and Movement Disorders Center at Northwestern University. All patients included in the
study were diagnosed by a movement disorders neurologist (TS) to have mild to moderate idiopathic PD (Hoehn and Yahr scale of II.5-III) (Hoehn and Yahr, 1967). Patients were tested in the morning after overnight withdrawal from antiparkinson’s medications (practically defined off medication state). Control subjects were matched in age (± 3 years) and gender to one of the PD subjects. Exclusion criteria for both groups included a history of significant cardiovascular, pulmonary, musculoskeletal, metabolic, or other neurological disorders, and a score of less than 26 on the Mini-Mental State Exam (Folstein et al., 1975). Subjects who were unable to independently ambulate without an assistive device were excluded. All subjects signed an informed consent form approved by the Northwestern University Institutional Review Board prior to participation.

Startling acoustic stimulus (SAS)

An analog tone generator (Grass Instruments, Model S10 CTCMA) was used to create the acoustic signal (1 kHz, 40 ms). The tone was amplified and presented via loudspeaker placed 50 cm behind the head of the subject. The peak intensity of the tone near the subject’s ears was approximately 124 dB (tested using a Bruel and Kjaer Impulse Precision Sound Level Meter, Type 2204).

Data collection

Ground reaction forces (GRFs) and moments were collected at a rate of 100 Hz from two force platforms (AMTI, Watertown, MA). Center of pressure (CoP) signals were derived from the forces and moments collected by the platforms. Bipolar surface electromyographic (EMG) signals were recorded bilaterally over the motor points of the tibialis anterior (TA), soleus (SOL).
muscles and from the sternocleidomastoid (SCM) ipsilateral to the stepping leg. EMG signals were preamplified at the skin surface (gain = 35) then further amplified and filtered (20–250 Hz) and sampled at 500 Hz using a National Instruments data acquisition board and custom data collection software (LabView 6.0, National Instruments, Austin, TX). All data were collected from 4 s before to 4 s after the presentation of the go-cue.

Protocol

Subjects stood on the force platforms with their feet placed a natural and comfortable distance apart. An outline of each foot was drawn on the floor to ensure foot placement was the same across trials. A visually-cued instructed-delay paradigm was used to examine the transition from stationary standing to the rapid initiation of forward stepping. Task instruction stimuli were presented to the subject using a horizontal array of light-emitting diodes placed at eye level 3 m in front of the subject (Figure 1A). During 45 visually-cued control trials, subjects received a pre-cue light presented for 100 ms followed 3.5 seconds later by an imperative go-cue light. Subjects were instructed to “think about stepping forward as fast as you can in response to the go-light” upon presentation of the pre-cue light and to initiate a series of three steps forward “as fast as possible” in response to the go cue light. In addition, they were instructed to not initiate the step before the go-light and to focus on anticipating and responding to the go-cue regardless of what happened during the trial. Subjects were reminded of these instructions periodically throughout the experiment. Subjects initiated the step with their dominant limb. In a total of 30 trials (40% of all visually-cued trials), a single SAS tone was presented between the pre-cue and the go-cue at one of six different time points: -1500 ms, -1000 ms, -500 ms, -250 ms, -100 ms, or 0 ms (Figure 1A). The timing of the SAS was randomized across trials and a total of 5 SAS
trials were collected at each time point. Data were inspected online after each trial to ensure that
the subject did not begin to lean forward after the presentation of the pre-cue. Trials in which
subjects leaned forward or stepped with the incorrect leg were discarded and repeated (0-3.5% of
trials). A total of 5 self-initiated trials were also collected in which subjects were instructed to
initiate stepping a fast as possible at any self-selected time following the verbal cue of
“Anytime”. Self-initiated trials were recollected if the subject immediately initiated the step in
response to the verbal instruction. In addition, 5 trials were also collected during which a SAS
was randomly delivered alone during inter-trial periods while subjects were not preparing to step.
These served as quiet standing (no movement preparation) SAS trials. The order of presentation
of the trials was partly randomized with the exception that a startle trial was not presented during
the first 5 trials and no more than 2 startle trials were presented in a row.

Data analysis
Data analysis was performed using customized software written in MatLab 6.0 (MathWorks
Inc., Natick, MA, USA). For dominant right limb steps, an APA was considered to be present if
the following components of the pattern were recorded (Brunt et al. 1991; Rogers et al. 2001;
MacKinnon et al., 2007): (1) an early EMG burst in TA prior to the onset of the voluntary step,
(2) an initial increase in the right foot vertical GRF, (3) an initial decrease in the left foot vertical
GRF, (4) an initial rightward shift in the CoP, and (5) an initial posterior shift in the CoP (Figure
1B). For dominant left limb steps, the vertical GRF and right-left CoP shifts were opposite to
those for right steps. Since a clear early suppression of SOL activity was not consistently
observed both within and between subjects, suppression of SOL activity was not considered to
be a requirement for the identification of an APA. The following parameters were measured for
each accepted right step trial (Figure 1B): (1) onset and offset times of the initial burst of TA
EMG activity and integrated EMG (IEMG) over that interval, (2) interval between the onset time
of the TA burst and the instant of the peak of the posterior excursion of the CoP and IEMG over
that interval, (3) times of the onset and first peak of the posterior excursion of CoP, (4) times of
the onset and first peak of the rightward and posterior excursion (leftward and posterior for left
steps) of CoP, (5) times of the onset and peak loading of the initial stepping leg GRF, and (6)
times of the onset and peak unloading of the initial stance leg GRF. GRFs were normalized by
expressing forces as a percentage of total subject weight. Onset times of EMG, CoP and GRF
changes were calculated based on changes of more than three standard deviations from the mean
signal recorded prior to the go-cue or acoustic stimuli and were verified by visual inspection and
adjusted manually as needed to coincide with the initial deflection of the signal from the baseline
level (Hodges and Bui, 1996).

Statistical analyses

Differences in the state of preparation of the APA between groups and over the time course
of the instructed-delay interval were examined by comparing the APA duration, magnitude and
incidence variables using a 2 × 6 repeated measures analysis of variance with a between-subjects
factor of Group (PD and Control subjects) and within-subject factor of SAS Timing (-1500, -
1000, -500, -250, -100, 0 ms). The proportion variables (e.g. incidence of APAs) were subjected
to an arcsine square root transform prior to the ANOVA. Greenhouse-Geisser corrected degrees
of freedom were used to correct for violations of the assumption of sphericity. Post hoc testing
of SAS Timing or Group × SAS Timing interaction effects were conducted using planned contrasts between adjacent time intervals with Bonferroni correction for multiple contrasts.

Group differences in the timing and magnitude of the APAs evoked across the cueing modalities (SAS, visually-cued and self-initiated) were examined using a 2 × 3 repeated measures analysis of variance with a between-subjects factor of Group (PD and Control subjects) and the within-subject factor of Cue Mode (SAS at 0 ms, visual cue, and self-initiated). Effects were considered to be significant at the p < 0.05 level.

**Results**

Representative examples of APAs in a patient with PD and a matched Control subject during a self-initiated trial, a visually-cued control trial, and three trials with a SAS (at -1500, -250 and 0 ms) are shown in Figure 2. In the patient with PD, self-initiated steps were associated with low amplitude and prolonged shifts in the CoP, negligible loading and unloading of the legs, and the TA EMG activity consisted of multiple small amplitude short bursts. In contrast, the self-initiated step in the Control subject showed a distinct APA pattern with a more fused TA EMG activity compared to the PD subject. The patterns of the GRF and CoP during visually-cued control trials were similar in both subjects, but the TA EMG in the patient with PD was characterized by discontinuous, short bursts of activity rather than the fused and continuous activity observed in the Control subject. Presentation of a SAS at 1500 or 250 ms before the go-cue evoked a small amplitude APA in both subjects with an EMG onset latency of less than 100 ms. Note that the direction of the shift in GRF and CoP was appropriate for the initiation of a right forward step (as planned by both subjects), but the sequence of activity necessary for toe-off was subsequently terminated before being reinitiated after the go-cue. When a SAS was
presented at the same time as the go-cue, an APA and stepping sequence was generated that was comparable in magnitude to the Control trial in both subjects, but the onset of the sequence was 80-100 ms faster than Control trials. Note that the TA EMG activity in the PD subject remained fractionated.

Incidence of early APAs evoked by a startling acoustic stimulus

Presentation of a SAS during the instructed-delay interval evoked the rapid release of an APA sequence that was appropriate for the initiation of a right forward step in an average of 94 ± 11% and 96 ± 8% of PD and Control subject trials respectively (Figure 3). When the stimulus was presented earlier in the delay interval (-1500 or -100 ms), APAs were evoked by a SAS in 3/5 to 5/5 of the trials (mean incidence: PD group = 89 ± 15%; Control group = 96 ± 9%). Later in the preparation interval (-500 to 0 ms) the incidence increased to 4/5 to 5/5 trials (mean incidence: PD group = 97 ± 7%; Control group = 96 ± 8%). There was no significant effect of Group (F(1) = 0.119, p = 0.736), SAS Timing (F(5) = 0.448, p = 0.664) or Group × SAS Timing interaction (F(1,5) = 0.862, p = 0.444) in the incidence of SAS-evoked APAs. When a SAS was presented between trials (during quiet standing), a sequence consistent with a right step APA was observed in less than 1% of all trials.

APAs were observed in all visually-cued control trials in all PD subjects and 97% of trials in the Control subjects. In contrast, APAs were frequently absent during self-initiated steps in the PD subjects (APAs were absent in 1 or more trials in 5 subjects). These trials were typically characterized by no preloading of the initial swing leg and no unloading of the stance leg during
the initiation of the step. However, it should be noted that an APA was absent during 2 of the 5 self-initiated trials in two of the matched control subjects. Comparisons across cueing modes showed a significant main effect of Cue Mode ($F(2) = 4.734, p = 0.036$) but no main effect of Group ($F(1) = 1.159, p = 0.301$) or Group $\times$ Cue Mode interaction ($F(1,2) = 1.653, p = 0.220$). Post-hoc tests showed that the incidence of APAs associated with self-initiated steps was significantly lower than the visual cued trials ($F(1) = 6.341, p = 0.026$) and marginally lower with a SAS at 0 ms ($F(1) = 4.225, p = 0.060$).

**Incidence of early forward steps evoked by a startling acoustic stimulus**

The APA evoked by a SAS during the instructed-delay interval was often immediately followed by a forward step. Subjects frequently commented that they were unable to withhold the action or that the forward step happened “spontaneously”, despite instructions to “not initiate the step before the go-light”. When a SAS was delivered at 0 ms, the APA was immediately followed by a forward step sequence in all trials in all subjects. The delivery of a SAS at -100 ms was associated with an immediate forward step in an average of 77% and 93% of trials in the PD and Control group respectively. In contrast, the average incidence of forward step release when the SAS was delivered between -1500 to -250 ms was less than 39% (incidence at -1500, -1000, -500, -250 ms: PD = 37, 34, 14, 34% ; Control subjects = 28, 38, 30, 35%). There was a significant main effect of SAS Timing on the incidence of forward steps initiated immediately following the SAS-induced APA ($F(5) = 37.804, p = < 0.001$), but no Group or Group $\times$ SAS Timing interaction effects ($p > 0.358$). Planned contrasts across SAS Timings showed that the
incidence of step release was not significantly different when a SAS was presented from -1500 to
-250 ms, but significantly increased at -100 ms (p < 0.001) and again at 0 ms (p < 0.002).

Timing and amplitude of APA responses evoked by a startling acoustic stimulus

The onset latency of the APA sequence evoked by the SAS was extraordinarily short in both
groups irrespective of the timing of stimulation. The average onset latency of the TA burst
relative to the SAS was 86.2 ± 7.2 ms and 92.4 ± 6.7 ms in the Control and PD groups
respectively (Figures 2, 4, 5). These latencies were an average of 89 ± 4 ms (PD) and 97± 3 ms
(Control group) earlier than the reaction times for the visually-cued Control trials. There was no
significant effect of Group (F(1) < 0.393, p > 0.542), SAS Timing (F(5) < 1.53, p > 0.328) or
Group × SAS Timing interaction (F(1,5) < 2.096, p > 0.077) on the onset timing of the TA burst,
GRFs or CoP excursions.

The state of preparation of the APAs was modulated over the instructed-delay interval as
reflected in changes in the amplitude and duration of the APAs evoked by the SAS across the
stimulation time points in both groups (Figures 4 and 5). Significant main effects of SAS
Timing were observed for the peak posterior and lateral CoP excursions, time to peak excursion,
peak loading and unloading GRFs, time to peak loading and unloading GRFs, magnitude of the
first TA EMG burst and TA IEMG from burst onset to the peak of the posterior CoP (F(5) >
4.524 , p < 0.001). Planned contrasts showed that there were three phases of preparation over the
1500 ms preparation interval tested in this study. During the first phase, from -1500 to -1000 ms,
the amplitude of the APA evoked by SAS was approximately 60-70% of the APA evoked by
stimulation at 0 ms. The second phase consisted of a significant decrease in the amplitude of all
measures of the APA between the -1000 and -500 ms time points (p < 0.013). The third phase
was characterized by an abrupt increase in amplitude and duration of the APA evoked by the SAS between the -250 and -100 ms time points (p < 0.01). Note that the three phases of preparation were observed in both the PD and Control groups.

Despite a similar time course of modulation during the preparation interval, the APAs evoked by a SAS in the subjects with PD were characterized by reduced amplitudes compared to the matched Control group (Figure 4). There was a significant main effect of Group for the peak lateral excursion of the CoP, stepping leg GRF (loading) and stance leg GRF (unloading) (F(1) > 4.88, p < 0.045), but not the posterior excursion of the CoP (F(1) = 0.640, p = 0.437). The lateral CoP and GRF amplitudes were consistently reduced across the instructed-delay interval in the PD group as shown by no significant Group × SAS Timing interaction effect (p > 0.370).

These differences in lateral CoP and GRF measures between groups could not be explained by differences in the initial stance width, as measured by the distance between the midpoints of the heels (PD = 17.9 ± 3.8 cm; Control = 19.2 ± 3.3 cm; two-tailed t-test t = 0.698, p = 0.503).

There were no significant Group or Group × SAS Timing interaction effects for the duration of the APAs (p > 0.113).

As described above, the TA muscle activation pattern in the patients with PD was characterized by short, fractionated bursts of activity, even for the APAs evoked by a SAS (Figure 5A). The initial burst of TA EMG activity associated with the SAS-evoked APAs was significantly shorter in duration in the PD group compared to the Control group (F(1) = 6.585, p
effects were observed for the lateral CoP and GRF variables, but an interaction effect was found for the posterior CoP excursion (F(1,2) = 3.475, p < 0.045). This interaction reflects the fact that the differences in posterior CoP excursion were observed for the visually-cued and self-initiated conditions (p < 0.012) but not with SAS at 0 ms condition (see Figure 4A).
There were significant main effects of Group (F(1) = 19.130, p = 0.001) and Cue Mode (F(2) = 6.265, p = 0.006) on the duration of the first TA EMG burst, but there were no Group × Cue Mode interaction effects. The duration of the first TA EMG burst was significantly shorter in the PD group (p = 0.001) across all cue modes. Post-hoc tests of the Cue Mode effects showed that the duration of the first burst was significantly longer for the visually-cued mode compared to both the SAS at 0 ms and self-initiated conditions (p < 0.021). No significant Group, Cue Mode or interaction effects were observed for the TA IEMG (from burst onset to peak posterior CoP) (Figure 5B).

Neck muscle activation by acoustic stimulation

The presence of a phasic, short-latency (<100 ms) neck muscle activation pattern due to the SAS was often absent or otherwise highly variable both within individual subjects and between different subjects. Hence, there was no clear or consistent pattern of a relationship between the SAS-evoked APA and neck muscle activation pattern indicative of a startle response.

Discussion

The main finding of this study was that the presentation of a SAS during the preparatory period of an instructed-delay task consistently resulted in the early release of the appropriate APA required to initiate forward stepping in patients with PD off medication. Furthermore, the temporal profile in the changes in APA magnitude and duration across the preparation period in the PD group was the same as the Control subjects. These findings demonstrate that patients with mild to moderate PD retain the capacity to prepare the spatial and temporal features of the APA well in advance of the intended timing of the forward step. However, the magnitude of the
APA was significantly reduced in the PD group throughout the preparation interval, demonstrating that the underscaling that characterizes voluntary movement in patients with PD (Pfann et al., 2001) is present during the preparation phase. The following sections will discuss these findings in the context of literature examining the effects of external cues on the facilitation of movement initiation in PD, the integration of posture and goal intended movement, and the pathways proposed to mediate these responses.

**APAs are released by a startling acoustic stimulus during movement preparation**

Our findings for patients with mild-to-moderate PD and healthy control subjects are consistent with previous studies of SAS-evoked movements observed in healthy younger adults showing that a SAS triggers the early release of the prepared motor sequence including the accompanying APAs. (Valls-Sole *et al.*, 1995, Valls-Sole *et al.*, 1999, Siegmund *et al.*, 2001, Carlsen *et al.*, 2004, MacKinnon *et al.*, 2007). APAs were reliably released in both PD (89% trials) and control subjects (96% trials) when a SAS was delivered as early as 1000 ms to 1500 ms prior to the go-cue. This high incidence of APA release during the preparation phase contrasts with the findings observed in young adults (MacKinnon *et al.*, 2007). Using a comparable instructed-delay task, the incidence of release in young adults was 40%, 64%, and 88% of trials when the stimulus was applied at -1400 ms, 100 ms, and 0 ms, respectively. The higher incidence of APAs evoked in both groups in the present study may reflect differences between studies in task instruction and subject attention. In the present study, subjects were instructed to “think about stepping forward fast as you can” following the pre-cue and then to initiate forward stepping “as fast as possible” in response to the go-cue, whereas no explicit instructions about the pre-cue were provided in the study with young adults. The addition of the
pre-cue instruction may have altered both the timing and magnitude of the preparation strategy. Increases in early premovement activity, as measured with EEG and faster reaction times, have been reported in both healthy adults and patients with PD when were instructed to anticipate the presentation of a predictably timed visual ‘go’ signal compared to when no such instruction was given (Cunnington et al., 1999; Cui and MacKinnon, 2009).

Age-related differences in habituation to the SAS are unlikely to have contributed to the high incidence of release of movement in patients with PD. Normally, the generalized startle reflex evoked during resting conditions is rapidly habituated over the course of only a few trials (Koch, 1999). Studies of the startle reflex in patients with PD have shown either reduced (Vidailhet et al., 1992, Nieuwenhuijzen et al., 2006) or normal habituation (Kofler et al., 2001). We observed that SAS-evoked responses in the neck muscles, indicative of a startle reflex, were consistently present only during the first few SAS trials when subjects were preparing to initiate stepping, but these responses were only intermittently present throughout the remainder of the experiment. In contrast, APAs were consistently released at latencies of less than 100 ms throughout the duration of the experiment.

Three distinct phases of movement preparation were identified in both groups. The first phase, from -1500 to -1000 ms prior to the onset of the imperative cue, was characterized by a SAS-evoked APA that was moderately large in amplitude (approximately 60-70% of the size of the APA observed with stimulation at 0 ms). These data show that the spatial and temporal parameters of the APA were planned and prepared early in the instructed-delay time period. This early preparation phase was followed by a phase of reduced APAs at the -500 and -250 ms time points. This suppression of planned APAs may reflect transient alterations in attention due to the long interval between the visual precue and go cue, analogous to the inhibition of return...
described by Posner and Cohen (1984), or an active inhibition of responses to prevent premature
initiation of the step sequence before the imperative cue. The suppression phase was followed by
an abrupt increase in the magnitude and duration of the APA evoked by a SAS in the time
interval immediately preceding the imperative cue (-100 to 0 ms). This finding is consistent with
our previous study (MacKinnon et al., 2007) which showed a marked increase in the magnitude
and incidence of SAS-evoked APAs when stimulation was applied immediately prior to, or
coincident with, the imperative cue. Since both studies used a fixed time interval between the
pre-cue and go-cue, these results demonstrate that the magnitude of the motor output for the
APA is increased late in the motor preparation interval when the timing of the imperative cue can
be predicted in advance.

A startling acoustic stimulus evokes APAs at very short latency

The APAs evoked by a SAS were further characterized by onset latencies that were an
average of 89 and 97 ms faster than the visually-cued control trials in the PD and control subjects
respectively. Moreover, TA EMG onset latencies of less than 100 ms were common in both
groups. Short latency responses have also been reported in patients with mild PD when a SAS
was delivered during different phases of the step cycle during treadmill walking

(Nieuwenhuijzen et al., 2006). Our findings provide evidence that the neuronal circuitry
mediating the speeded initiation of postural adjustments is intact in individuals with mild to
moderate PD.

APAs are reduced in magnitude in patients with PD
Despite a spatial and temporal profile of APA preparation that was comparable to the Control group, the magnitude of the APA sequence was consistently attenuated across all SAS-Timing and Cueing Mode conditions in the patients with PD. During movement preparation, variables related to medial-lateral shifts in the APA, including the peak rightward CoP excursion and loading and unloading GRFs, were significantly reduced. Interestingly, no significant differences were observed between groups in the peak posterior excursion of the CoP during movement preparation, but a significant attenuation of this variable was seen during visually-cued and self-initiated movements. The EMG profile in the TA muscle was characterized by a reduced duration of the initial phasic activation and an abnormally discontinuous muscle recruitment pattern. These differences in postural adjustment characteristics with PD resembled similar observations reported in previous studies of step initiation (Crenna and Frigo, 1991, Gantchev et al., 1996, Burleigh-Jacobs et al., 1997, Vaugoyeau et al., 2003, Mille et al., 2007, Jacobs et al., 2009). The marked reduction in APA amplitude is also consistent with studies showing that voluntary movements in patients with PD are characterized by impaired scaling of forces and muscle activity and an EMG pattern that is distinguished by multiple short bursts of muscle activity rather a fused agonist contraction (Pfann et al., 2001; Robichaud et al., 2009).

Our data further shows that impaired scaling of APAs in the PD group could be detected as early as 1500 ms before the go-cue and persisted throughout the preparatory interval. Nonetheless, they retained the capacity to modulate the magnitude of postural preparation in a manner similar to the Control group. This finding indicates that the patients with PD were capable of planning and preparing the postural accompaniments of stepping well in advance of an expected external cue to initiate gait, but the planned APA was reduced in magnitude.
It is conceivable that the differences in APA characteristics between the groups could be attributable to differences in step speed rather than to pathophysiological processes. For gait initiation, the amplitude and duration of the early sagittal plane CoP changes for forward propulsion do vary with gait speed, while the frontal plane APAs for lateral weight transfer and stability are independent of gait speed (Breniere and Do, 1986; Breniere et al., 1988). For both Control and Self-Initiated trials, we found a generalized reduction in A-P and M-L APA amplitudes with PD, whereby the speed insensitive frontal plane amplitude reduction was statistically more robust than the speed sensitive sagittal plane reduction. Furthermore, the SAS triggered frontal plane APAs were smaller in amplitude for PD patients while the sagittal APAs were not different from controls. This suggested a differential involvement of APA preparation in the frontal plane compared with the sagittal plane that was not likely dependent on the speed of stepping. Furthermore, APA duration of mechanical variables was not different between the groups for either APA component. The reduced magnitude of the IEMG bursts in the TA ankle muscles for PD subjects mainly reflected a reduced activation duration due to the abnormal fractionization or discontinuity of muscle activation (Figure 2) rather than differences in activation due to step speed.

Self-initiated movements are preferentially impaired in PD and improved with external cues

In keeping with previous studies (Burleigh-Jacobs et al., 1997), APAs in the PD patients were increased in duration and decreased in magnitude during the self-initiated trials compared with the cued Control condition and trials with a SAS at 0 and -100 ms. Most importantly, APAs are frequently absent (~20% of trials) during self-initiated stepping. It is also noteworthy that APAs were also frequently absent in the age-matched older control subjects. It is well known...
that external sensory cues can improve voluntary movement performance, including gait
initiation in patients with PD (Martin, 1967; Rubinstein et al., 2002). For example, providing
visual, acoustic, or somatosensory stimuli can enhance the magnitude and duration of the APA
during gait initiation as well as increase the speed and distance of the step component (Burleigh-
Jacobs et al., 1997, Dibble et al., 2004, Jiang and Norman, 2006, Mille et al., 2007). Moreover,
the improvements in APAs with external cues can be observed in the off medication state
(Burleigh-Jacobs et al., 1997), suggesting that sensory signals facilitate movement via
mechanisms that are largely independent of dopaminergic pathways. Similarly, we found that a
simple visual go-cue (Control trials) significantly enhanced APAs compared to the self-initiated
trials in patients off medication. Additionally, our results demonstrate that APAs can be elicited
at very short latency by a strong external sensory cue when the stimulus is presented early during
the preparation interval of an instructed-delay task. However, the effectiveness of the cue on
enhancing motor performance is likely dependent upon the timing of the stimulus with respect to
the expected timing of the imperative go-cue (Cui and MacKinnon, 2009). When a SAS was
presented between 1500 and 250 ms prior to the go-cue, the evoked APA was not significantly
different from the self-initiated trials, whereas stimulation at -100 and 0 ms evoked APAs were
indistinguishable from visually cued trials. Thus, the timing of delivery of the sensory cue with
respect to the intended timing of movement initiation can have a marked affect on the magnitude
and duration of the evoked movement release.

The mechanisms by which external cues improve the initiation of movement in patients
with PD are poorly understood. It has been hypothesized that sensory cues facilitate movement
via parietal-dorsal premotor cortical (Passingham, 1987, Samuel et al., 1997, Sabatini et al.,
2000) or cerebello-thalamocortical (Glickstein and Stein, 1991) pathways that are independent of
Accordingly, it has been proposed that external cues facilitate the initiation of movement via pathways that mediate reactions to external sensory stimuli and thus bypass processes associated with abnormal motor preparation (Morris et al., 2001). Alternatively, external cues may serve to enhance the preparation of movement. Consistent with this idea, a variety of studies have shown increased movement-related activity in the regions of the lateral premotor and parietal cortex in patients with PD (Samuel et al., 1997, Praamstra et al., 1998, Catalan et al., 1999, Sabatini et al., 2000). Studies in healthy young adults have shown that movement tasks that are paced by a set of fixed intervals cues are associated with early preparatory activity in the region of the lateral premotor cortex (Praamstra et al., 2006). Moreover, the magnitude of this preparatory activity is markedly enhanced when subject attempt to respond at the time of the imperative go-cue compared to self-initiated, self-paced movements (Cui and MacKinnon, 2009). Thus, the instructed-delay paradigm used in the present study may provide a method to reliably enhance movement preparation and facilitate step initiation in patients with PD via premotor pathways that are predominantly independent of the basal ganglia.

Conclusions

In summary, this study showed that the presentation of a loud acoustic stimulus during an instructed-delay period prior to stepping triggered the early and rapid release of the prepared postural adjustments for weight transfer and forward propulsion in patients with PD (off medication) and healthy controls. Moreover, the spatial and temporal profile of preparation in the PD groups was indistinguishable from the Control group. However, the amplitude of APA evoked by a SAS was attenuated in the PD group, demonstrating that impaired scaling of APAs is present during the preparation phase. These results provide evidence that patients with PD are...
capable of planning and preparing an APA for step initiation well in advance of an expected cue to initiate gait. In addition, the findings show that, with advanced instruction to focus attention on the intended movement and the timing of the forthcoming go-cue, external cues can significantly improve gait initiation in patients with PD.

ACKNOWLEDGMENTS

We wish to thank the volunteers who participated in these experiments and Mr. Di Zhang and Mr. Fang Gao for their technical expertise and computer programming.
FIGURE CAPTIONS

Figure 1. A. Schematic diagram of the timing of the pre-cue and imperative go-cue visual stimuli and the delivery of six startling acoustic stimulus probes. B. Examples of the TA EMG, CoP, and GRF variables measured to quantify the timing and magnitude of the APA. The vertical arrows indicate the time points of the onset and termination of the first TA burst, onset and peak of the initial CoP excursions, and onset and peak of the GRF changes. Note that the TA EMG was integrated both from the onset to the end of the first burst, and from the start of the burst to the time of the peak posterior displacement of the CoP (vertical dotted line).

Figure 2. Examples of APAs during right stepping trials in a patient with PD (top) and a matched control subject (bottom). In both subjects, the visually-cued control trials (2nd column plots) were characterized by a burst of activity in TA, increased loading and unloading of the stepping and stance legs respectively, and rightward and posterior displacement of the CoP. Note that the EMG in the patient with PD was fractionated into short bursts. Self-initiated steps (1st column plots) were associated with small short duration bursts of activity in the TA and low magnitude and prolonged duration of APAs in the patient with PD. The presentation of a SAS at -1500 ms (3rd column plots) resulted in a brief burst of EMG activity approximately 100 ms after the stimulus and accompanying small shifts in the GRF and CoP, consistent with APA initiation, then termination for a planned right forward step in both subjects. This was subsequently followed by the initiation of a second APA and accompanying forward step in response to the go-cue light. The presentation of a SAS at 0 ms (coincident with the go-cue) resulted in an APA pattern remarkably similar to the visually-cued control condition, yet the onset was
approximately 100 ms earlier. The vertical dashed lines indicate the timing of the imperative go-
cue for the visually-cued control trials and timing of the tone delivery for the SAS trials.

**Figure 3.** The average incidence of trials in which an APA was observed that was appropriate
for the generation of the intended step, irrespective of APA magnitude. PD - black bars; Control
subjects - white bars. CON = visually-cued control trials; SI = Self-initiated trials.

**Figure 4.** Summary of the CoP (A) and GRF (B) measures of APAs across subjects and
between groups (PD – black bars or squares; Control subjects – white bars or circles). The top
plots in A and B show the time from the onset (reaction time) to the first peak of the APA
measure. Onset times are expressed relative to the timing of the SAS delivery for conditions S1
to S6 and relative to the onset of the imperative light cue for the visually-cued control trials
(CON). The onset time for the self-initiated (SI) condition was set to 0 ms. The lower plots in A
and B show the peak amplitude of the APA variable across conditions. SAS Timing: S1 = -1500
ms, S2 = -1000 ms, S3 = -500 ms, S4 = -250 ms, S5 = -100 ms, S6 = 0 ms.

**Figure 5.** Summary of the TA EMG data across subjects and between groups (PD – black bars
or squares; Control subjects – white bars or circles). A. Onset time and duration of the first TA
burst. Onset times are expressed relative to the timing of the SAS for conditions S1 to S6 and
relative to the imperative light cue for visually-cued control trials (CON). The onset time for
self-initiated (SI) condition was set to 0 ms. B. Profile of changes in TA EMG magnitude.

EMG was integrated from the onset of the first TA burst to the peak posterior excursion of the
CoP. SAS Timing: S1 = -1500 ms, S2 = -1000 ms, S3 = -500 ms, S4 = -250 ms, S5 = -100 ms,
S6 = 0 ms.
REFERENCES


Passingham RE. Two cortical systems for directing movement. Ciba Found Symp. 1987;132:151-64.


Table 1. Patient Characteristics

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Mean ± 1SD

|       | 67 ± 9 | 5.8 ± 3 | 26 ± 6 |

SD = standard deviation, N/A = not available; LE = Levodopa equivalent daily dose.