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Compensatory stepping in Parkinson’s Disease is still a problem after Deep Brain Stimulation randomized to STN or Gpi

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Running head: Reactive Stepping Responses in Parkinson’s Disease.

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Abstract

The effects of Deep Brain Stimulation (DBS) on balance in people with Parkinson’s Disease (PD) are not well established. This study examined whether DBS randomized to the subthalamic nucleus (STN, n=11) or globus pallidus interna (GPi, n=10) improved compensatory stepping to recover balance following a perturbation. The standing surface translated backwards, forcing subjects to take compensatory steps forward. Kinematic and kinetic responses were recorded. PD-DBS subjects were tested off and on their levodopa medication before bilateral DBS surgery, and retested six months later off and on DBS, combined with off and on levodopa medication. Responses were compared with PD-control subjects (n=8) tested over the same time scale and 17 healthy control subjects.

Neither DBS nor levodopa improved the stepping response. Compensatory stepping in the best-treated state after surgery (DBS+DOPA) was similar to the best-treated state before surgery (DOPA) for the PD-GPi group and the PD control group. For the PD-STN group, there were more lateral weight shifts, a delayed foot-off and a greater number of steps required to recover balance in DBS+DOPA after surgery, compared to DOPA before surgery. Within the STN group, 5 subjects who did not fall during the experiment before surgery fell at least once after surgery, whereas the number of falls in the GPi and PD-control groups were unchanged.

DBS did not improve the compensatory step response needed to recover from balance perturbations in the GPi group and caused delays in the preparation phase of the step in the STN group.

Keywords: Deep Brain Stimulation, Parkinson’s Disease, balance, compensatory stepping.
Introduction

The large number of falls experienced by people with Parkinson’s Disease (PD) (Pickering et al. 2007) are thought to be related to inadequate postural responses (Bloem et al. 2001; Horak et al. 1996; Horak et al. 2005). The ability to generate a step quickly and accurately after a loss of balance is disrupted in PD and levodopa medication seems to offer no benefit (King et al. 2008; King et al. 2010). This study investigated whether Deep Brain Stimulation (DBS) randomized to either the globus pallidus interna (GPI) or subthalamic nuclei (STN) could improve the compensatory stepping response of people with PD.

DBS has been shown to have significant anti-parkinsonian effects that are superior to best medical therapy by reducing the cardinal PD symptoms including tremor, bradykinesia and rigidity (Weaver et al. 2012; Weaver et al. 2009). However, there have been mixed results on whether quantitatively measured balance is also improved. Some aspects of balance control, such as postural sway when standing show improvement when DBS is turned on (Rocchi et al. 2002). In-place postural responses also improve when DBS is turned on compared to off DBS, however when compared to pre-surgery function there is no overall improvement, with STN-DBS showing worsening compared to GPI-DBS (St George et al. 2012). Voluntary step initiation does not improve with DBS and there is an overall impairment in step preparation after surgery compared to before surgery in both STN and GPI sites (Rocchi et al. 2012).

When taking a voluntary step forward, a lateral weight-shift toward the stance foot (sometimes called an anticipatory postural adjustment or APA) is required to maintain lateral balance when the stepping foot is off the ground. When a predictable external perturbation pushes a standing person just beyond the threshold of an in-place response, an APA is generally observed just prior to the compensatory step. However as the perturbation increases in strength or becomes unpredictable, the APA is increasingly absent in healthy control
subjects (McIlroy and Maki 1993). The side-ways instability induced by taking one foot-off
the ground is given less priority than the forward instability imposed by the perturbation and
so the lateral APA is inhibited in order to expedite the compensatory step to preserve balance.
When subjects with PD are exposed to large, unpredictable perturbations, they exhibit APAs
far more frequently than control subjects, which delays the time to lift the stepping foot (King
et al. 2010). Furthermore, PD subjects sometimes make multiple APAs before a
compensatory step, as though they are preparing to lift a particular foot-off the ground only to
abort and switch to the other foot. This behavior is associated with festination and freezing of
gait (Jacobs et al. 2009), and freezing of gait in PD is associated with falls (Kerr et al. 2010).
The execution phase of the compensatory step is also affected in PD (King et al. 2010). A
step that is too short may be insufficient to arrest the falling center of mass (CoM) of the
body, so subsequent steps may be required to recover balance. Similarly, a step that is too
slow may allow the CoM to fall further in the time before the foot contacts the floor, again
subsequent steps may be required.
The primary aim of this study was to determine whether the DBS procedure in either STN or
GPi, could improve the stepping responses of PD subjects to fast, unexpected postural
perturbations. Step preparation and execution phases were studied in PD subjects before, and
6 months following DBS surgery. Both off and on levodopa medication, and off and on DBS
states were tested to determine interaction effects between the therapies. A PD control group
was tested to compare any changes to the natural progression of PD over the six-month time
frame.
Materials and Methods

Subjects

Seventeen healthy control subjects and 29 subjects with idiopathic PD were included in this study. The healthy control group included 14 men and 3 women with an average age of 65.7 (S.D. 7.7) years. Twenty-one of the PD subjects underwent DBS surgery. Target DBS sites were randomized to either the STN (n=11) or the GPi (n=10) as part of a VA/NINDS multicenter, double-blind clinical trial (Follett et al. 2010). The 8 remaining PD-control subjects met the criteria for DBS surgery, but chose not to undergo the procedure. There were no significant demographic differences between the groups (Table 1). All subjects gave informed written consent for protocols approved by the Institutional Review Board of Oregon Health & Science University.

[Table 1]

Surgical Procedure

Bilateral surgical implantation of DBS electrodes (Medtronic, 3387) was performed by an experienced neurosurgeon (author KB) using a Leksell stereotactic frame and MRI guidance (STEALTH FrameLink). Using the NeuroTrek system (Alpha-Omega, Atlanta, Georgia) two microelectrodes were advanced simultaneously and recordings made for the purposes of target verification and corrections to the implant site were made if needed. For further details see St George et al, 2012 (St George et al. 2012). DBS subjects visited a movement disorders neurologist on at least three occasions over 90 days for DBS and medication optimization. The mean amplitude of the DBS was 3.29V (range 1.4 to 5V), with 80% of the subjects having a 90µm pulse width (4 subjects at 60µm), and at a rate of 185Hz for 70% of the subjects, the others ranged between 130 and 150Hz.
Experimental protocol:

Subjects stood on dual force plates of a moveable platform looking straight ahead (Figure 1). Arms were folded across the chest to ensure consistency between subjects and to allow visibility of the motion analysis markers on the greater trochanter. Trials took place after a series of slower-velocity forward and backward platform translations. Three trials began with foot width parallel and 5 cm apart, another three trials at 26 cm apart and a final trial at a self-selected comfortable width. Initial analysis revealed no significant effect of these three foot displacements between treatment conditions so responses were averaged across the seven trials. A harness attached to the ceiling was worn which did not provide support in upright stance, but would catch the subject midway through a fall. An assistant stood behind the subject and only intervened when it was clear the subject could not regain standing equilibrium independently. The location of the center of pressure was monitored prior to each trial on an oscilloscope and the perturbation only began when the center of pressure was in the subject’s quiet stance range. Subjects were instructed to keep their balance as best they could. Platform translation was backwards at a velocity that pilot testing had revealed was above stepping threshold of young control subjects (step velocity profile of 56cm/s for 0.5s). Therefore the only way to recover equilibrium without assistance was to initiate a compensatory stepping response.

Experimental conditions:

Baseline: Compensatory stepping responses of PD-DBS and PD-control subjects were tested in the morning in the “practical” OFF state - at least 12 hours since taking any dopaminergic medication. Later the same day they were retested when they reported feeling “ON”
medication after waiting between 45 and 75 minutes after taking their usual dose of dopaminergic medication.

6 months: PD-DBS subjects were retested six months after DBS surgery to allow the effects of surgery to stabilize (Burchiel et al. 1999). These subjects again arrived at the laboratory in the practical-off medication state with their DBS on. Following testing in the DBS only condition, the stimulator was turned off and after 45-60 minutes subjects were retested in the OFF/OFF condition. Subjects then took their usual antiparkinsonian medication dose and were retested approximately an hour later on medication (DOPA). In the final condition, the stimulator was turned on and approximately 30 minutes later testing was performed in the DBS+DOPA condition. The PD-control subjects were retested six months later with the baseline test protocol.

Before each condition, PD subjects were tested on the motor subsection of the Unified Parkinson’s disease Rating Scale (UPDRS III) (Fahn and Elton 1987;St George et al. 2014). Plenty of rest and refreshment breaks were offered throughout the testing session.

Data collection and analysis:

A 3D representation of body motion was measured using the Motion Analysis system (Santa Rosa, CA) with 8 video cameras recording 23 reflective markers placed on body landmarks at 60 Hz. Step latency was determined from the time of surface translation to the time the weight on the stepping foot dropped to below 2% of body weight. The vertical forces under the feet were assessed for the presence of APAs prior to stepping. An APA was only identified if a mediolateral force shift toward the stepping foot and away from the stance foot occurred before foot lift off and at least 50 ms after the perturbation onset (Figure 1B) (King et al. 2010). Centre of body mass (CoM) was calculated from joint positions and
anthropomorphic measurements (Vaughan et al. 1982). The number of steps required to arrest
the falling CoM were recorded.

[Figure 1]

**Statistical Analysis**

The number of APAs before foot-off were compared between groups and conditions with
non-parametric statistics. The normally distributed foot-off latency, CoM position at foot-off,
mean number of steps, and the length and velocity of the first step were compared between
groups and conditions with multivariate repeated measures analysis of variance. The
statistical tests were implemented according to the specific comparisons of interest.

- **Disease effect**: comparison between the healthy control subjects and PD subjects at
  baseline were performed using group (healthy control / PD control / PD-GPi / PD-
  STN) as a between subjects factor.

- **Procedural effect**: comparison between baseline and the 6 month assessment when off
  and on medication for the three PD groups (PD-control, PD-STN, PD-GPi).

- **Stimulation and therapy interaction effects**: after DBS surgery the effect of DBS
  (on/off) and medication (on/off) on the stepping variables for the STN and GPi groups
  were compared.

- **Therapeutic effect**: the best-treated state at baseline (DOPA) was compared to the
  best-treated state at the 6-month retest (DOPA for the PD controls and DOPA+DBS
  for the PD-DBS subjects).

Spearman correlations were calculated to determine the association between the number of
APAs prior to foot-off and the other step parameters.
Results

Disease effect: At baseline assessment, there was no difference in any of the stepping variables between the PD control, PD STN and PD GPi groups (p>0.05 for each post-hoc comparison). Figure 2A shows that lateral APAs before foot-off occurred more frequently in subjects with PD compared to control subjects (p<0.01). In 90% of trials healthy control subjects had no APA prior to foot-off, whereas PD subjects at baseline had one or more APAs on approximately one third of trials. The time to take the stepping foot-off the ground and the displacement of the CoM were similar between control and PD groups at baseline (Figure 2B and 2C). The first compensatory step was longer (p<0.01) and faster (p=0.045) for healthy control subjects compared to subjects with PD (Figure 3A and 3B). In addition, subjects with PD required a greater number of total steps to regain balance compared to the healthy controls (p<0.01, Figure 3C).

Procedural effect: When comparing baseline OFF and DOPA conditions with six month OFF and DOPA conditions across PD groups, there was no significant change in the number of APAs prior to stepping, the foot-off latency, the displacement of the CoM at foot-off, or the velocity of the step. Step length of the first step was shorter at the 6-month assessment compared to baseline assessment (p=0.04) but there was no session by PD group interaction (p=0.913) suggesting natural progression of disease was the cause. There was a significant session by PD group interaction (p=0.037) for the total number of steps, as the STN group required more steps to recover balance than they did before surgery (p=0.029), whereas the GPi and PD-control groups had no change (p>0.05 for each). Medication did not affect any of the stepping variables, with no significant main or interaction effects.
Stimulation and therapy interaction effects: When comparing the four conditions at 6-month assessment in the DBS groups the preparation phase of the step appeared to be negatively affected by turning the stimulator on in the STN group, but not the GPi group. The number of APAs prior to foot-off increased from about one third to a half of all trials when the DBS was turned on compared to off (Figure 2A) for the STN-DBS subjects (p=0.021). In contrast the number of trials with APAs remained unchanged for the GPi-DBS group when DBS was turned on. There was a significant stimulation (DBS off, DBS on) by group interaction for stepping latency (p=0.05) with the DBS stimulation increasing stepping latency more in the STN than GPi. The length and speed of the first step and the number of total steps was not changed by turning the stimulator on and there were no length or speed interaction effects with DBS group.

Therapeutic effect: The number of APAs prior to the step increased in the best-treated state after surgery (DBS+DOPA) compared to the best-treated state (DOPA) at baseline for the STN group (p=0.017), but not the GPi or PD-control group (Figure 2A). There was a significant best-therapy (baseline, 6 months) by group interaction for step latency (p=0.041) and CoM displacement at foot-off (p=0.043) and the number of steps (0.017). This interaction was because the STN group had longer step latencies, a further CoM at foot-off and a greater number of average steps required to recover balance at the 6 month assessment than they did at baseline.

APA correlations: A greater number of APAs prior to foot-off was associated with delayed step latency (R=0.39, p<0.001), an increased CoM displacement at foot-off (R=0.37, p<0.001), reduced step length (R=-0.1, p=0.001), reduced step velocity (p=-0.11, p<0.001) and an increase in the total number of steps required to recover balance (R=0.23, p<0.001).
Falls: When subjects failed to independently recover balance this trial was classified as a fall (always caught by the harness or researcher). Within the STN group, 5 subjects who did not fall before surgery experienced at least one fall after surgery, whereas the number of falls in the GPi group were either unchanged or improved (Table 2).

[Table 2]

Discussion

Deep Brain Stimulation in either the STN or GPi did not improve stepping responses to external perturbations. The results showed that step latency, step speed, step length and the total number of steps did not improve for either group six months after DBS surgery. In fact, DBS in the STN disrupted the postural preparation phase, with more lateral weight shifts prior to foot-off, which led to delays in executing the step.

Perturbations to the body during standing may be overcome with a feet-in-place response for small perturbation forces, however as the perturbation force increases, a protective step must be executed to prevent a fall. Previously we showed that turning DBS ON improved the feet-in-place postural response for both STN and GPi stimulation sites (St George et al. 2012). In contrast, the current study revealed that turning the DBS stimulator on actually impaired the compensatory stepping response in the STN group and made no change for the GPi group. In light of these findings, there appears to be fundamental differences in the control of in-place and compensatory stepping responses. It is thought that in place postural responses are more automatic and controlled at the brainstem level, whereas stepping responses are less automatic, longer latency and involve a level of cortical control (Jacobs and Horak 2007). For the in-place response there is no switching of tasks, i.e. subjects began standing and the task was to remain standing. However, when the in-place response is no longer sufficient to
maintain balance there must be a switching of motor programs from a bilateral symmetric
postural response to an asymmetrical step initiation.

A lateral APA prior to the compensatory forward step occurred infrequently for control
subjects, whereas subjects with PD had difficulty inhibiting the APA. The occurrence of
APAs prior to a step indicate that a decision to step had been made. More frequent lateral
weight shifts prior to foot-off may indicate a deficit in coupling the postural preparation for
the step and the execution of the step itself. An emerging concept from this work is that the
delay to initiate a compensatory step in PD could be due to a failure to inhibit the lateral
APA, compounded with impairment in transitioning from the APA to the leg-lift. The failure
to switch quickly to the most appropriate motor program for large perturbations may be due
to a response inhibition problem in people with PD.

Impulsive behavior and motor inhibition are generally worse in people with PD compared to
healthy control subjects (Obeso et al. 2011; Cohen et al. 2014), and levodopa medication
does not improve these problems (Obeso et al. 2011). The STN is well placed for a role in
suppressing thalamocortical output, via the hyperdirect pathway, in order to inhibit unwanted
motor responses (Aron and Poldrack 2006). DBS of the STN does appear to affect inhibitory
motor control, but the literature disagrees on whether STN DBS is detrimental or beneficial.
When DBS is turned “on” response inhibition is worse compared to DBS “off”, as assessed
by the Stroop test (Witt et al. 2004) and go/no-go tasks (Ballanger et al. 2009; Hershey et al.
2004). In the stop-signal task (SST), where the movement response must be halted during
preparation or execution phases, some studies have shown STN DBS enhances inhibitory
control by shortening the SST reaction time of arm (Mirabella 2012) and finger movements
(Van den Wilden 2006, Swann 2011). Other studies demonstrate more complex interactions.
Ray et al. show that STN DBS improves inhibitory control in patients with initially worse
SST compared to control subjects, however when SST was initially in the range of control
subjects, inhibitory responses are impaired by STN DBS (Ray, 2009). Furthermore, while proactive inhibition is reported to be enhanced by STN DBS (Mirabella 2013, Obeso 2013), reactive inhibition is worsened (Obeso, 2013). Together, the literature suggests that the STN affects motor inhibition through parallel pathways, which may have positive or negative effects depending on the context and the nature of the motor task.

The results of this study showed that turning the STN DBS on prolonged the initial in-place postural response before switching to the more appropriate stepping response. This delay was not evident in GPi DBS. Unfortunately there are no studies of the effect of GPi DBS on inhibition of upper limb movements to compare with our findings. Our results indicate there may be differential effects of STN and GPi stimulation on response inhibition in postural tasks.

Turning the stimulator on in the STN group seemed to affect the preparation phase of the step more than the execution phase, as the number of APAs increased, which in turn delayed stepping time and resulted in greater CoM displacement. In contrast, the length and speed of the first step in the STN DBS group were similar whether DBS was on or off. This suggests that DBS may be more involved in coordinating the timing between the postural and stepping programs than with the step execution itself. Although the step length and speed were not changed by DBS in STN, given that the CoM was further forward when the step was made, the step size and speed should have been scaled up to make an appropriate compensatory response. The initial step was not sufficient to halt the body’s forward motion and this explains the need for a greater number of steps. The failure to scale the postural response appropriately may be more related to the PD, rather than the DBS. It is known that people with PD have difficulty scaling motor output according to postural feedback (Kim et al. 2009).
Five (45%) of the STN group fell more after surgery than before, whereas there was no change in the falls incidence in the GPl group. This result may help explain the higher incidence of more serious falls in the STN DBS group than the GPl DBS group, in the larger multi-center trial, of which these subjects were a subset, (Follett et al. 2010).

A limitation of the study was the fixed sequence of conditions: DBS, OFF, DOPA, DBS+DOPA. This sequence was chosen to allow PD DBS subjects to be tested over a single day, however it is possible that stepping responses improved with practice. However, as the final condition (DBS+DOPA) showed worsening in the STN group it suggests that the DBS was detrimental over and about any practice effect that may have occurred.

STN DBS is often associated with a reduction in levodopa medication dose, but in the present study there was no significant reduction. The clinician who consulted with the subjects for treatment optimization may have had a cautious medication reduction approach. Although medication dose was routinely reduced if medication-induced dyskinesias were problematic, dyskinesia cannot be ruled out as a potential confounder. On the other hand, because medication dose remained similar across PD groups and between baseline and 6-month assessments, confounding effects of medication dose variability were minimized.

**Conclusions**

The human balance system needs to be flexible and continuously adaptable to new conditions. The ability to inhibit and switch between motor responses quickly, and to scale the motor output appropriately is affected in PD. The results of this study show that neither levodopa medication nor DBS treatments were able to improve the flexibly of the balance system in PD. In fact, there was evidence that DBS stimulation in the STN prolonged inhibition of the in-place response, thereby delaying the transition to the compensatory stepping response.
Acknowledgments

We thank Drs. Penelope Hogarth and Ali Saami for referring subjects from the OHSU and Seattle, respectively and Triana Nagel for assisting with data acquisition.

Grants

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References


Figure Legends

Figure 1. The subject stood quietly with arms folded (Ai) when the standing surface unexpectedly moved backwards with a step velocity that forced the subject to make a compensatory step forward (Aii). Examples of vertical force distribution changes under the feet during the perturbation and the categorization of anticipatory postural adjustments (APA) are shown in B.

Figure 2. Preparation for compensatory stepping. The percent of trials categorized by their APA behavior for each of the groups (A). Mean (±S.E.) of: the latency to the foot-off (B), and forward displacement the CoM at the time of foot-off (C) for each condition. In B and C, the PD control group is shown in black, the PD-GPi group is white, the PD-STN group is gray and the healthy control (HC) group is shown in pale gray.

Figure 3. Execution phase of compensatory stepping. Mean (±S.E.) of: the length of the first step (A), the average velocity of the first step (B), and the total number of steps required to regain balance for the PD-control subjects (C). The PD control group is shown in black, the PD-GPi group is white, the PD-STN group is gray and the healthy control (HC) group is shown in pale gray.
### Tables

#### Table 1: Demographics of the PD groups and clinical characteristics

<table>
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<th>STN (n=11)</th>
<th>PD-Control (n=8)</th>
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<td>7M 1F</td>
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<td>PD duration (yrs)</td>
<td>15.4 ± 8.7</td>
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*UPDRS III

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<tr>
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<th>baseline off</th>
<th>baseline DOPA</th>
<th>6m off</th>
<th>6m DOPA</th>
<th>6m DBS</th>
<th>6m DBS+DOPA</th>
<th>*LEDD: baseline</th>
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<tr>
<td></td>
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<td>908.4 ± 538</td>
<td>1149± 345</td>
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All errors are standard deviations unless otherwise stated.

*Total Unified Parkinson’s Disease Rating Scale III

*Levodopa Equivalent Daily Dose (Nutt et al. 2003).
Table 2. The percentage of trials in which the subject fell.

<table>
<thead>
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<th>Site</th>
<th>Baseline</th>
<th>6 months</th>
<th>stimulation</th>
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<tr>
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<td>Off DOPA</td>
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<td>DBS DOPA+DBS%</td>
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<tr>
<td></td>
<td>%</td>
<td>%</td>
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<tr>
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<td>0 0 43 0 43</td>
<td>185Hz, 2.6V</td>
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<tr>
<td>STN</td>
<td>0 0</td>
<td>0 14 0 0</td>
<td>185Hz, 3V</td>
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<tr>
<td>GPi</td>
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<td>NA 43 43 43</td>
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<tr>
<td>GPi</td>
<td>0 14</td>
<td>0 0 0 0</td>
<td>150Hz, 3.8V</td>
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</tbody>
</table>

*Only subjects who fell are shown. All other subjects did not fall for any trials.*
Ai

Aii

B

- platform velocity
- 56 cm/s
- stance foot
- step foot
- foot-off

i. no APA

ii. 1 APA

iii. multi APA

iv. multi APA with no foot-off

weight change (N)

0

0

0

0

0

0

0

0

0

0

200 400 600

time (ms)