Neural correlates of impaired motor timing processing during speech production and hand movement in Parkinson's disease

Roozbeh Behroozmand[1], Karim Johari[1], Priyantha Herath[2], Jeremy Greenlee[3]

[1] Speech Neuroscience Lab, Department of Communication Disorders, University of South Carolina, [2] Department of Neurology, University of South Carolina, [3] Departments of Neurology and Neurosurgery, University of Iowa

Introduction

Background:

Parkinson's disease (PD) is a neurodegenerative neurological disorder resulting from progressive cell death of dopaminergic neurons in the basal ganglia[1]. A hallmark of PD is demonstrated by patients' impairment in processing the temporal aspects of sensory stimuli for movement, which can have detremental effects on their speech and limb motor function capabilities[2-5]. However, the underlying neural bases of such motor timing impairment in PD has remained poorly understood.

Evidence from previous studies suggests that the temporal aspects of extrernally presented sensory stimuli can modulate motor reaction time during tasks involving starting[6,7] and stpping[8,9] movement. These studies have indicated faster motor reaction time in response to temporally predictable vs. unpredictable sensory stimuli. This finding was discussed in the context of a predictive coding model in which an internal representation of timing is established to facilitate movement.

Objective:

The present study was a systematic investigation toward understanding the effects of PD on temporal processing mechanisms of movement in speech and hand motor systems. Our goal was to use objective measures of motor reaction time in response to external sensory stimuli with temporally predictable and unpredictable intervals to address the following questions:

1– How the temporal aspects of sensory stimuli affect motor response reaction time during initiation and inhibition of speech and hand movement in PD patients?

2– What are the neurophysiological correlates of temporal processing modulation in response to predictable and unpredictable sensory stimuli in patients with PD?

Methods

Subjects:

We recruited 15 right-handed non-demented PD patients (5 females, mean age: 66.4 yrs) and 15 neurologically intact control (7 females, mean age: 63.9 yrs). At the time of testing, PD patients had a mean disease onset of 4.1 years (std: 1.5) and all were clinically stable with mild-to-moderate motor impairments (UPDRS Part III mean score 13.56, std: 3.6, range: 6–19). The mean upper limb hypokinesia was assessed at 5.5 (std: 1.93) in PD based on finger tapping and rapid alternating hand movement items in Part III of the UPDRS battery . Patients were tested on-medication with individually tailored dosages of dopaminergic medication (e.g., Levodopa) prescribed by their own neurologists. For each patient, Levodopa Equivalent Dose (LED) was obtained by adding the LED for each anti-parkinson medication. Theoretically, LED of a medication can be defined as the level at which the equivalent improvement in motor symptoms would be observed as for 100 mg immediate Levodopa release. PD patients and control subjects had no history of psychiatric disorder, vision or hearing impairments.

Methods

Experimental task:

The experiment consisted of two random-order tasks of speech production and hand movement. Subjects prepared to perform one of the motor tasks following the onset of a relevant visual cue on the screen (**Fig. 1**). During each task, subjects were instructed to prepare for the cued movement and start vocalizing the speech vowel /a/ or pressing a button after a circle (GO signal) appeared on the screen and stop after the circle disappeared (STOP signal). We designed two counterbalanced blocks within which the subjects performed the tasks in response to temporally predictable and unpredictable visual stimuli.

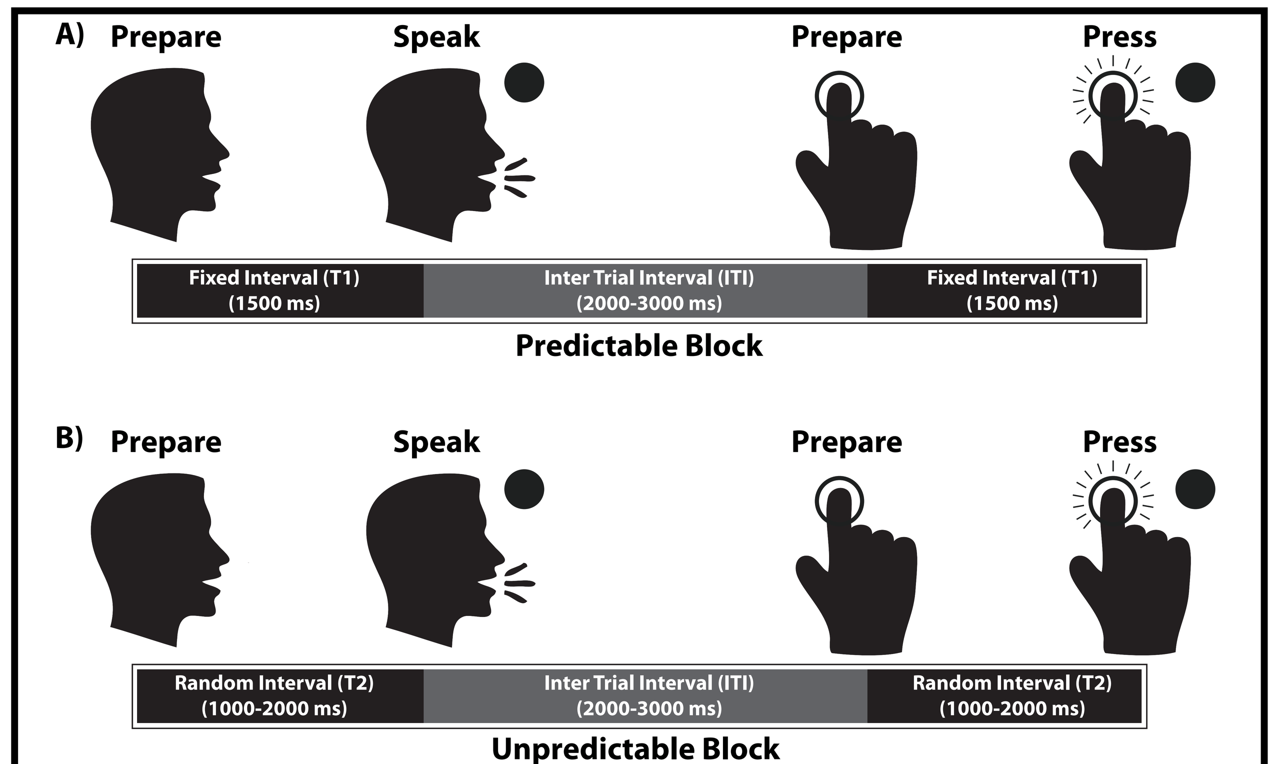

Figure 1. Experimental design of the motor reaction time task for A) temporally predictable and B) unpredictable blocks. In each block, subjects were presented with a task-relevant visual cue (hand or speech) and were instructed to prepare to press a button or vocalize the vowel /a/ after a circle (go signal) appeared on the screen and stop after it disappeared. In this figure, T indicates the time interval between "Preparation" and "Go" in either button press or vocalization task. For the predictable block, the time interval (T1) was fixed at 1500 ms, whereas for the unpredictable block, the time interval (T2) was randomized between 1000-2000 ms. ITI represents the inter-trial-interval which was about 2-3 seconds for both predictable and unpredictable conditions.

EEG recording:

The EEG signals were recorded from 64 electrodes using the BrainVision active electrode system (Brain Products GmbH, Germany) placed on a standard cap with standard 10-20 montage. A BrainVision actiCHamp amplifier (Brain Products GmbH, Germany) on a computer utilizing Pycorder software recorded the EEG signals at 1 kHz sampling rate after applying a low-pass anti-aliasing filter with 200 Hz cut-off frequency.

EEG analysis:

The EEGLAB toolbox (https://sccn.ucsd.edu/eeglab) was used to analyze EEG signals to extract event-related potentials (ERPs) time-locked to the onset of speech and hand movement for temporally predictable and unpredictable stimuli. EEG signals were first filtered offline using a band-pass filter (1-30 Hz, –24 dB/oct) and then an ICA was applied to remove eye movement, blinks, muscle, and line noise artefacts. The signals were then segmented into baseline corrected epochs ranging from –300 to 500 ms (baseline at -300 to -200 ms). Extracted epochs were then averaged across all trials to obtain ERPs for each condition, separately.

Statistical analysis:

For each modality, mixed-model ANOVAs were implemented to examine the effects of group (PD vs. control), stimulus timing, and task on ERPs and behavioral measures of speech and hand motor reaction time.

Results

Behavioral responses:

Results indicated slower reaction times in PD vs. control. Both groups showed faster responses for stopping vs. starting movement (**Fig. 2**).

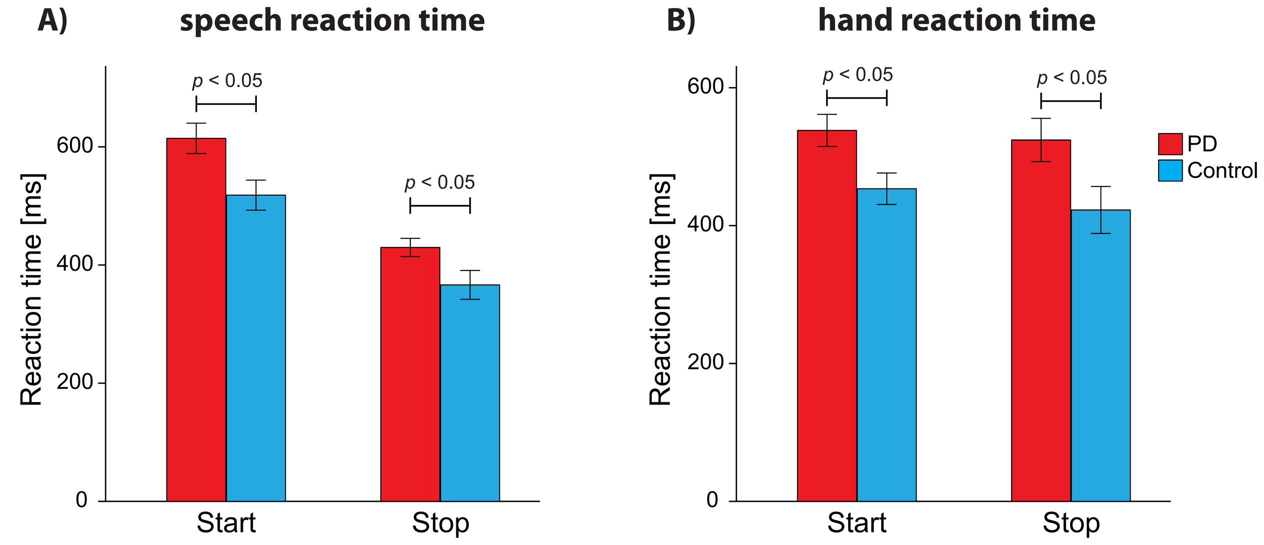

Figure 2. Behavioral measures of motor reaction time for the start and stop of **A)** speech production and **B)** hand movement in PD patients vs. neurologically intact control subjects.

There was no difference between PD and control in response to unpredictable stimuli. However, when stimulus timing was predictable, control subjects exhibited faster reaction times. No such effect was observed for PD patients (**Fig. 3**).

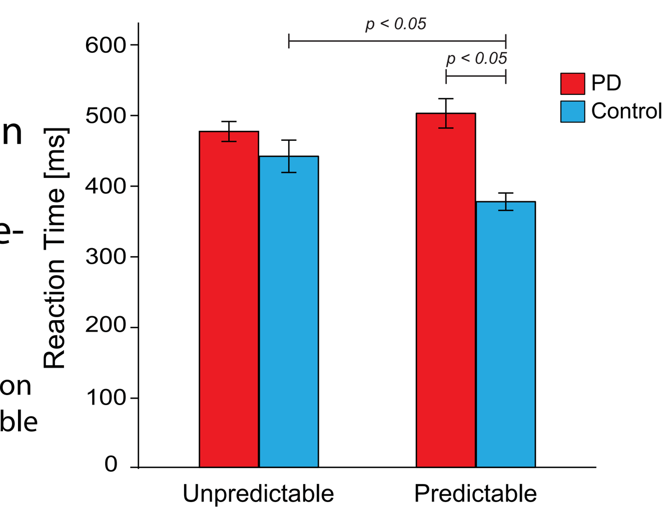

Figure 3. Behavioral measures of motor reaction time in response to unpredictable vs. predictable stimuli in PD vs. control.

ERP responses:

Premotor ERPs were significantly diminished ($p<0.05$) for starting and stopping speech and hand movement in PD vs. control subjects (**Fig. 4**).

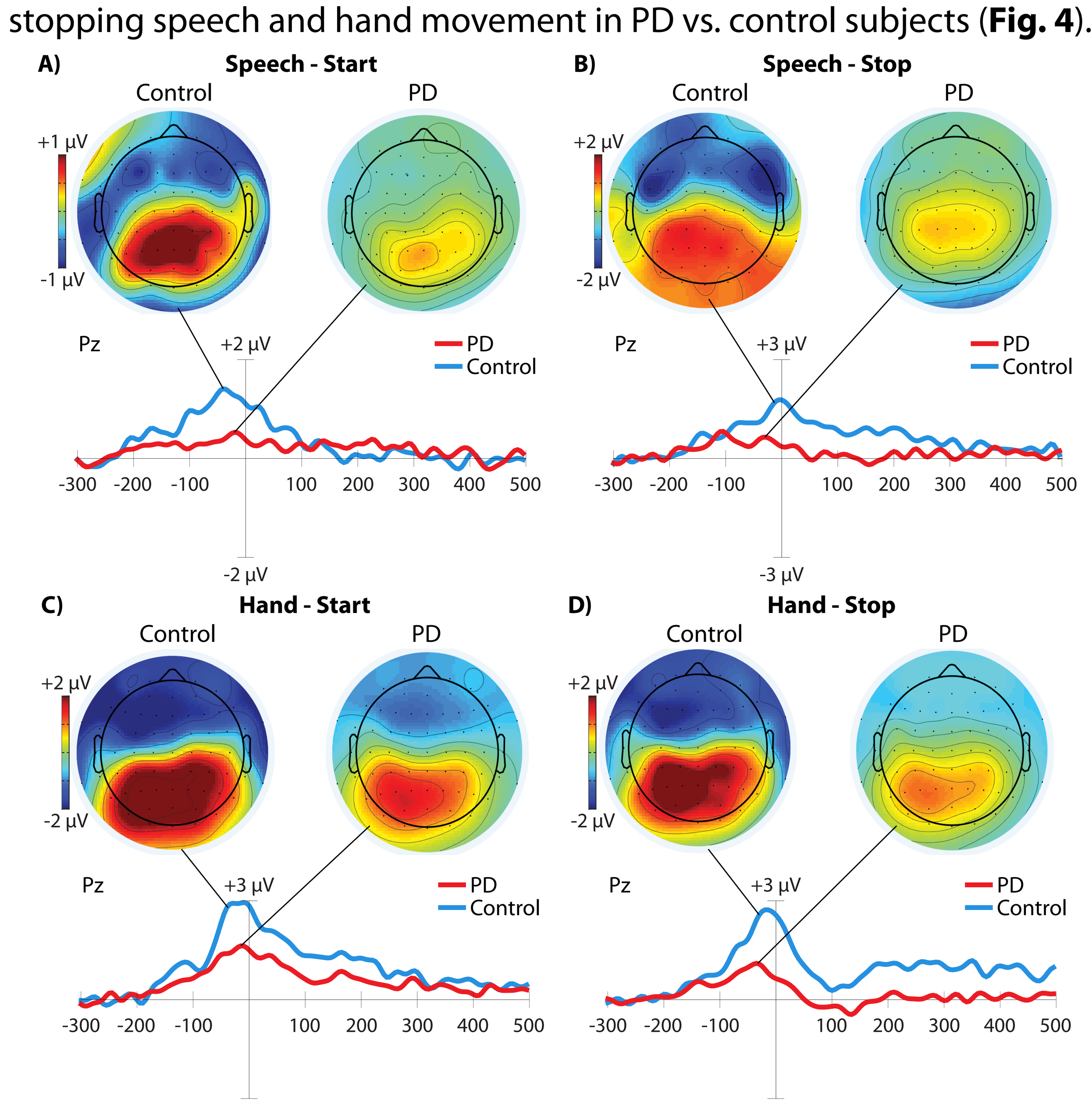

Figure 4. The overlaid profiles of ERPs responses and topographical maps across PD and control groups for **A)** speech start, **B)** speech stop, **C)** hand start, and **D)** hand stop movement conditions.

Discussion

Our novel approach led to the identification of the neural correlates of impaired motor timing processing during speech production and hand movement in patients with Parkinson's disease.

We propose that our findings support the following notions:

Patients with Parkinson's disease have deficits in starting and stopping their speech and hand movement, as indicated by their slower motor reaction time in response to sensory stimuli compared with control individuals.

Our findings indicate that Parkinson's disease is associated with impairment of temporal predictive mechanisms that establish internal representations to facilitate motor function in response to predictable stimuli. This notion is supported by our data showing that when control subjects performed the speech and hand movement tasks, their motor reaction time was significantly improved in response to temporally predictable stimuli. However, patients with Parkinson's disease did not exhibit such improvement in their motor performance when stimulus timing was predictable.

We propose that impaired motor timing processing in Parkinson's disease is reflected by the attenuation of premotor components of ERP activities in speech and hand modalities. This notion is corroborated by our data showing that the amplitude of pre-motor ERPs were significantly reduced before starting and stopping speech production and hand movement in PD patients compared with controls.

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