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Alterations in Oropharyngeal Sensory Evoked Potentials (PSEP) with Parkinson's disease

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Abstract

Movement of a food bolus from the oral cavity into the oropharynx activates pharyngeal sensory mechanoreceptors. Using electroencephalography, somatosensory cortical-evoked potentials resulting from oropharyngeal mechanical stimulation (PSEP) have been studied in young healthy individuals. However, limited information is known about changes in processing of oropharyngeal afferent signals with Parkinson's disease (PD). To determine if sensory changes occurred with a mechanical stimulus (air-puff) to the oropharynx, two stimuli (S1-first; S2-second) were delivered 500 ms apart. Seven healthy older adults (HOA; 3 male and 4 female; 72.2 $\pm$ 6.9 years of age), and thirteen persons diagnosed with idiopathic Parkinson's disease (PD; 11 male and 2 female; 67.2 $\pm$ 8.9 years of age) participated. Results demonstrated PSEP P1, N1, and P2 component peaks were identified in all participants, and the N2 peak was present in 17/20 participants. Additionally, the PD participants had a decreased N2 latency and gated the P1, P2, and N2 responses (S2/S1 under 0.6). Compared to the HOAs, the PD participants had greater evidence of gating the P1 and N2 component peaks. These results suggest that persons with PD experience changes in sensory processing of mechanical stimulation of the pharynx to a greater degree than age-matched controls. In conclusion, the altered processing of sensory feedback from the pharynx may contribute to disordered swallow in patients with PD.

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TP: Experimental design, assisted in the running of experiments, analyzed data, and assisted in manuscript preparation.

KWH: Experimental design, assisted in the running of experiments, analyzed data, and prepared the manuscript.

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DCB: Experimental design and prepared the manuscript.

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Additional Keywords

Swallow; dysphagia; mechanical; pharynx

Introduction

In persons with Parkinson's disease (PD), dysphagia can result from motor or sensory abnormalities (Born et al., 1996; El Sharkawi et al., 2002; Hunter et al., 1997; Miller et al., 2006; Mu et al., 2012; Pitts et al., 2009; Pitts et al., 2008; Pitts et al., 2010; Potulska et al., 2003; Robbins et al., 1986; Troche et al., 2010; Troche et al., 2008). Throughout the progression of PD, up to 100% of individuals experience some form of dysphagia and aspiration pneumonia is a leading cause of death in these patients (Akbar et al., 2015; Martinez-Ramirez et al., 2015; Pennington et al., 2010). Aspiration can be caused by uncoordinated movements or significant delays in the initiation of the swallow (Hammond and Goldstein, 2006; Kendall and Leonard, 2001; Logemann et al., 2008; Martin et al., 1994; Martinez-Ramirez et al., 2015).

Swallow is initiated by stimulation of the oropharyngeal wall, and the afferent information is processed by cortical and subcortical structures including the brainstem, pons, thalamus, primary sensory cortex, and limbic structures (Bosma, 1957; Davenport et al., 2011; Doty, 1968; Doty and Bosma, 1956; Gestreau et al., 1996; Gow et al., 2004; Hartnick et al., 2001; Hukuhara and Okada, 1956; Jean, 1984; Kennedy III and Kent, 1988; Kern et al., 2001; Saito et al., 2002; Sumi, 1967; Umezaki et al., 1997; Vantrappen and Hellemans, 1967). The cerebral cortex is thought to be important in sensory processing, attention, and the affective process of the stimulus (Ashraf et al., 2008; Babiloni et al., 1999; Chan and Davenport, 2008; Colon et al., 1983; Crowley and Colrain, 2004; Davenport et al., 2007; Davenport et al., 1996; Davenport et al., 2000; Davenport et al., 1986; Desmedt et al., 1983; Folstein and Van Petten, 2008; von Leupoldt et al., 2013). To evaluate this sensory system, an air-puff was applied to the oropharyngeal wall and cortical sensory evoked potentials (EP) were recorded from the scalp using electroencephalography (EEG) (Wheeler-Hegland et al., 2010, 2011). Wheeler-Hegland, et. al. (2011) established in young healthy adults that there is cortical processing of pharyngeal mechanical stimulation, termed oropharyngeal sensory evoked potential (PSEP). Additionally, this technique can evaluate whether the processing of the information changes during a paired stimulus paradigm (500 ms interval), termed sensory gating (Chan and Davenport, 2009, 2010; Chan and Davenport, 2008; Wheeler-Hegland et al., 2010).

Sensory gating is a process by which redundant sensory information is inhibited from reaching the cortex (Chan and Davenport, 2010; Chan et al., 2012; Chan and Davenport, 2008; McCormick and Bal, 1994; McCormick and Bal, 1997). The thalamus is thought to be one of the most important neuroanatomical substrate responsible for sensory gating (Gaudreau and Gagnon, 2005; McCormick and Bal, 1994), and has been hypothesized to be part of the suprapontine areas involved in swallowing (Mosier and Bereznaya, 2001). During sleep, rhythmic burst firing inhibits the vast majority of sensory information from reaching the cortex, yet during wakefulness, single spike activity allows the thalamus to have finer

control (McCormick & Bal, 1994; McCormick, 1992). Projections from the thalamus are processed in layer IV of the somatosensory cortex, which in turn has extensive projections to the thalamus. This establishes a feedforward and feedback system, creating a cortical-thalamic loop to prevent the cortex from being flooded by redundant sensory information (McCormick and Bal, 1994; McCormick and Bal, 1997). In this loop, the thalamus acts as a “gate,” allowing the primary stimulus to reach the cortex while inhibiting subsequent or redundant information. Wheeler-Hegland (2010) provided evidence of limited gating of the PSEP in young healthy adults, and more specifically that central processing of mechanical stimulation to the pharyngeal wall is different than other somatosensory modalities i.e. respiratory-related (Chan and Davenport, 2009; Chan and Davenport, 2008) and auditory (Korzyukov et al., 2007) which have significant suppression of the second stimulus event. We hypothesize that limited gating of pharyngeal mechanical stimulation is advantageous for effective airway protection, due to the time-course of the pharyngeal phase of swallow and the ability of humans to perform sequential swallow tasks. This current project tests the hypothesis that since sensory evoked potentials have been used as diagnostic indicators of PD (Boecker et al., 1999; Di Lazzaro et al., 1999; Rossini et al., 1989), significant decreases in the latency and gating ratios of the PSEP component peaks would be found.

Methods

Participants

The Institutional Review Board at the University of Florida approved the study (IRB 1113–2008). Twenty participants were recruited for this study: seven healthy older adults (HOA; 72.2 ± 6.9 years of age), and thirteen participants with idiopathic PD (67.2 ± 8.9 years of age). The diagnosis of PD was made by a fellowship-trained movement disorders neurologist according to the United Kingdom (UK) brain bank criteria. Participants were tested on their prescribed PD/non-PD medication(s). All participants self-reported no history of head or neck cancer, neurologic disease (except for idiopathic PD), chronic respiratory diseases, history of smoking within the last 10 years, or dysphagia. Participants were asked to refrain from caffeine intake for at least twelve hours prior to the study, due to the known effects of caffeine on evoked potentials (Connors, 1979; Emerson et al., 1988; Tharion et al., 1993; Wolpaw and Penry, 1978).

Oropharyngeal Sensory Evoked Potentials (PESP)

The PSEP protocol was conducted according to the technique of Wheeler-Hegland and colleagues (Wheeler-Hegland et al., 2010, 2011). Participants were seated comfortably with the back, neck and head supported. A 32-electrode Neuroscan Quickcap™ (based on the International 10–20 system) was positioned on the participant’s head and connected to the SynAmps² Neuroscan System. Electro-conducting gel was applied through each electrode in order to establish scalp contact and maintain impedance levels below 5kΩ. Bipolar electrodes were placed on the skin above and below the left eye for recording vertical electro-oculogram (VEOG) activity. Synamps amplifiers (Neuroscan, El Paso, TX) and SCAN version 4.3 acquisition software (Neuroscan, El Paso, TX) were used to record the EEG signal onto a desktop computer. The EEG activity was referenced to linked earlobes. The sampling rate was set to 1000 Hz per channel with an applied bandpass filter of DC to

200 Hz. SCAN version 4.3 analysis software (Neuroscan, El Paso, TX) was used for data analysis (see below).

A certified clinically competent speech-language pathologist (CCC-SLP) administered the air-puff protocol (author, TP). A mouthpiece with a polyethylene tube was placed in the mouth, and a flexible laryngoscope was inserted through the tube (identical to Wheeler-Hegland et al (2011) Figure 1). The laryngoscope images were displayed, but not recorded, on a computer screen. Both the laryngoscope and computer were components of the JEDMED StrobeCAM II® system (JEDMED Instrument Co., St Louis, MO). In this manner, the laryngoscope allowed for visualization and verification of tube placement for air-puff delivery. The laryngoscope itself was covered with a hygienic sheath (Slide-On® Sheath for Sensory Testing, Medtronic Xomed, Inc., Jacksonville, FL) that has a small port through which the air-puffs were delivered. The port was connected to an air tank, connected to a solenoid valve, which delivered air-puffs through the laryngoscope tube. When a second investigator (author KH) triggered a solenoid valve, air under positive pressure was delivered through the tubing onto the participant's pharyngeal surface. Two air-puffs (S1, first stimuli; S2, second stimuli) were delivered with an inter-stimulus interval of 500 ms. The pressure was regulated at approximately 20–30 cm H₂O. Of note, the pressure varied depending on the participant's relative comfort, without triggering a cough, swallow or gag. Each air-puff was delivered for approximately 150–200 ms. A 750 ms EEG and pressure sample epoch was recorded from the onset of the air-puff pressure. A total of 256 EEG epochs of air were presented. To ensure limited muscle contraction of the face and neck, the participants were intermittently asked to relax and not bite down on the mouthpiece. Additionally, to reduce Alpha –rhythms, the participants were asked to keep their eyes open and watch a movie.

Of note, the participants with PD verbally expressed more discomfort with the study protocol and had greater difficulty suppressing reflexes (cough, swallow and gag) than the older healthy adult participants. However, there was no protocol in place to measure these responses.

Data Analysis

Analysis was blinded for the participant group. During offline analysis, the EEG data was reviewed frame-by-frame with the following inclusionary criteria: a) stable pre-stimulus baseline, b) no VEOG eyeblink activity, and c) EEG waveform did not exceed 50 uV. Following the sorting, at minimum 190 EEG epochs were used for analysis. Then the Scan 4.3 software determined the EEG amplitude at and between all the electrodes. This, along with visualization of the S1 and S2 waveforms and 2-D head models, allowed for identification of the positive and negative component peaks. Figure 1a demonstrates the P1 (first positive), N1 (first negative), P2 (second positive) and N2 (second negative) identified component peaks. Next, the recording electrode closest to the area of greatest positive or negative EEG amplitude was identified as the hot spot. Note, if the electrode site with the greatest magnitude for a peak (hot spot electrode) was different between S1 and S2, the closest common electrode was chosen.

To determine if sensory gating occurred with the mechanical stimulus to the pharynx, the two stimuli were delivered with a 500 ms interval (S1 and S2). The amplitude of the S2

PSEP component peaks were divided into the S1 PSEP component peaks, which gave a gating ratio (S2/S1) (Figure 3). Ratios less than 0.6 are considered positive for gating, i.e. the smaller the ratio the more significant the gating of the S2 peak.

A Mann-Whitney U Test was performed to compare the S2/S1 ratio (Figure 3) and S1 latency for the P1, N1, P2, and N2 component peaks across the two groups (PD & HOA) using IBM® SPSS® Statistics 22.0 (Armonk, New York) due to the unequal sample sizes.

Results

Pharyngeal Stimulation Evoked Potentials (PSEP)

The mechanical stimulus to the pharynx resulted in four evoked potential peaks (P1, N1, P2 and N2; Figure 1). P1, N1 and P2 component peaks were present in all participants, and the N2 was present in 6/7 of the older healthy adults and 11/13 of the participants with PD. See Table 1 for mean and standard deviation (SD) of all S1 PSEP latencies. There was a significant decrease in N2 S1 peak latency comparing the PD (160 ± 20 ms) to the HOA (211 ± 41 ms; $p = 0.003$) participant group. Additionally, the hot spot locations for all the component peaks across all participants are graphically displayed in Figure 2, on the International 10–20 system.

Sensory Gating

On average, the PD group gated the P1, P2, and N2 peaks, and the HOA gated the P2 peak. Figure 3 illustrates the gating ratio from each participant for each component peak, and Table 1 reports the average group gating ratios. Comparing the gating ratios, the PD group significantly gated (i.e. lower gating ratios) the P1 [PD (0.59 ± 0.41); HOA (1.26 ± 0.91); $p = 0.05$] and N2 [PD (0.27 ± 0.24); HOA (0.88 ± 0.68); $p = 0.02$] component peaks (Table 1) than the HOAs.

Discussion

The aim of this study was to examine the effect of PD on pharyngeal somato-sensation using the PSEP protocol (Wheeler-Hegland et al., 2010, 2011). P1, N1, P2 component peaks were identified in all study participants, while N2 peaks were present in 85% (17/20) of the total participants. Additionally, the PD participants had a significant decrease in the N2 latency compared to the HOA. Finally, cortical gating was exhibited in the P1, P2 and N2 component peaks in the PD participants and the P2 in the HOAs. More specifically, the PD group had statistically significant increases in gating for the P1 and N2 compared to the HOA. This is evidence of significant changes in the central processing of mechanical stimulation to the pharynx with PD.

Evoked potentials (EPs) are the nervous system's electrophysiologic response to sensory stimuli (Colon et al., 1983; Nunez, 2006; Nunez and Srinivasan, 2006). EPs are indicative of cortical activity in response to stimulation of afferent fibers. A localizable stimulation created a cortical EP (Ashraf et al., 2008; Babiloni et al., 1999; Babiloni et al., 2009; Davenport et al., 2007; Davenport et al., 1996; Davenport et al., 2000; Davenport et al., 1986). Stimulation types include mechanical stimuli (air-puffs or touch), auditory stimuli

(clicks), or electrical stimuli (nerve stimulation). In addition, respiratory-related EPs have been studied using an inspiratory occlusion paradigm (brief occlusions are applied on the inspiratory phase of respiration) that increases the breathing effort and this results in consistent EP responses (Davenport et al., 2007; Davenport et al., 1996; Davenport et al., 2000; Davenport et al., 1986).

The P1 is indicative of the arrival the afferent stimulus at the cortex (Davenport et al., 1996; Desmedt et al., 1983; Nunez, 2006). Davenport, et al. (1996) hypothesized that the P1 reflects change in cortical activity from a dipole within the somatosensory cortex, similar to the respiratory related EP P1 and the sensory EP P50 from mechanical stimulation to the hand and leg (Chan and Davenport, 2008; Desmedt et al., 1983). It also suggests cortical awareness of the pharyngeal stimuli, which is not dependent upon the participants attending to the stimuli (Davenport et al., 1986; Williamson, 1990).

The source localization for each peak was also of interest (Figures 1 and 2). The hot spot locations, though a gross measure of source localization, does provide limited information in regards to the source of the dipole. The hot spot locations for the PSEP P1 were all from posterior central or lateral placements. This is similar to what von Leupoldt and colleagues (2010) reported: the respiratory-related EP P1 cortical source was the centro-parietal region.

The N1 peak reflects initial cortical processing of somatosensory stimuli, and can be affected by attention to the stimulus, as well as changes in the magnitude of the stimulus (Davenport et al., 2007). The oropharyngeal air-puff elicited various sensations including urge to swallow, cough and gag. In fact, Wheeler-Hegland, et al. (2011) examined urge-to-cough, in response to the same pharyngeal air-puff stimulation in young adults, and found that 68% of air-puff trials elicited an urge-to-cough response. Thus, due to the placement of the scope and the sensations reported, it is unlikely that the participants were able to ignore the stimulus throughout the experiment. The majority of N1 hotspot locations were located across the midline electrodes (17/20; Figure 2). This is similar to other sensory modalities. The respiratory related EP N1 is maximal over the vertex of the central somatosensory region when reference to the joined ear lobes was used (Webster and Colrain, 2000a, b). Additionally, EPs in response to an auditory stimulus also report vertex negativity at approximately 130 ms (Rushby and Barry, 2009). These results demonstrate that the PSEP N1 is similar to N1 vertex peaks recorded from other sensory stimuli.

The P2 peak was present in all participants. Until recently the P2 has been viewed as part of the N1 component peak. However, Crowley and Colrain (2004) advocate that the P2 is independent because the respiratory related EP P2 has an independent response to the rise time of the respiratory occlusions (Revelette and Davenport, 1990). The P2 has also been shown to be affected by the participant attending the stimulus (Crowley and Colrain, 2004; Webster and Colrain, 2000b).

The N2 peak is influenced by cognitive control, more specifically strategic monitoring and response to the stimulus (Folstein and Van Petten, 2008; Rushby and Barry, 2009). The PSEP N2 peak was not present in all participants; this has been noted in other event-related

potential studies i.e. Ritter and colleagues (1979), who stated that in cases where a strong P2 is elicited it can obscure the N2.

In other sensory modalities gating of sensory EPs is a hallmark of cortical processing (Arnfred et al., 2001; Chan and Davenport, 2008; Kinsley et al., 2001). In contrast, Wheeler-Hegland and colleagues (2010) reported that in young healthy adults there was no significant gating of PSEP component peaks. It was hypothesized that due to the nature of swallow there is a need for continuous afferent feedback; and if this feature is disrupted, it could lead to dysphagia. In the present study the PD group, on average, had significantly lower gating ratios for the P1 and N2 peaks, however, the HOA on average gated the P2 response (Figure 3; Table 1). This is evidence of change in the processing of sensory afferent information, and could represent challenges to sequential swallow tasks (swallows taking place < 500 ms apart). A vast majority of studies have reported changes in oropharyngeal reflexes with age and disease (e.g. swallowing, laryngeal adductor response, and cough) (Aviv et al., 1999; Aviv et al., 1996; Aviv et al., 1997; Aviv et al., 2002; Ebihara et al., 2003; Fontana et al., 1998; Troche et al., 2010; Troche et al., 2008), and this current study is evidence of a possible mechanism for these reported changes.

Recent work from the Arizona Parkinson's disease Consortium has demonstrated altered pharyngeal muscle and sensory nerves with the progression of PD (Mu et al., 2012, 2013a, Mu et al., 2013b). This includes atrophic muscle fibers, alterations in fiber type grouping, and transformation of myosin heavy chain from fast-to-slow (Mu et al., 2012). Additionally, when they examined the glossopharyngeal nerve, pharyngeal branch of the vagus nerve, and the inferior superior laryngeal nerve, there was evidence of pathology in all PD patients (Mu et al., 2013b). This is the first evidence of PD directly affecting sensory afferents.

Conclusions

The oropharyngeal stimuli elicited event-related potentials (P1, N1, P2, and N2) in a population of HOA and those with PD. Significantly lower gating ratios for the P1 and N2 peaks were present within the participants with PD when compared to the HOA. This is additional evidence that the oropharyngeal afferents and sensory processing of mechanical stimulation of the pharynx are changed with PD. Additional studies are needed to determine if the PSEP component peaks could be used as a screening or diagnostic device to allow for earlier treatment of dysphagia.

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Highlights

Use of a paired air puff stimuli to the pharynx to determine changes in sensory processing with Parkinson's disease.

Changes in the PSEP and gating response are potential mechanisms for dysphagia in Parkinson's disease.

The timing of repetitive swallow might necessitate a lack of gating pharyngeal mechanical stimulation.

Figure 1.

A. Example of a pharyngeal sensory evoked potential (PSEP) waveform. The component peaks P1, N1, P2, and N2 are labeled. **B.** The hot spot electrode was determined using the waveform and two-dimensional map. Positive charge is characterized in red, and negative charge is characterized in blue.

Figure 2.

Incidence of hot spot location of each PSEP (P1, N1, P2 and N2) graphically displayed on the International 10–20 system. The incidence scale on the left represents the number of participants who had their hot spot at that location.

Figure 3.

Gating of the PSEP response across the 4 component peaks (P1, N1, P2 and N2) (S2/S1) results from each of the participants (PD-left; HOA-right). Gray dotted line represents the cut-off for determination of a gated response. Note the N2 component peak was missing in participants 9 (PD), 14 (PD), and 20 (HOA).

Table 1

Mean and standard deviation (SD) of the gating ratio (S2/S1) and the S1 latency from the PD and HOA groups. Group comparisons were made with the Mann-Whitney U Test.

Gating Ratio	P1		N1		P2		N2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PD	0.59 ±	0.41	0.70 ±	0.55	0.38 ±	0.35	0.27 ±	0.24
HOA	1.26 ±	0.91	0.62 ±	0.31	0.34 ±	0.30	0.88 ±	0.68
<i>p</i> -value		0.05		1.0		0.69		0.02
S1 Latency								
PD	61 ±	16	93 ±	17	122 ±	16	160 ±	20
HOA	70 ±	19	101 ±	25	152 ±	39	211 ±	41
<i>p</i> -value		0.39		0.31		0.18		0.003

Bold *p* value 0.05 is considered significant

Italics cortical gating ratio's under the 0.6 threshold