Short-term neurophysiological effects of sensory pathway neurorehabilitation strategies on chronic poststroke oropharyngeal dysphagia

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Abstract
Background: Neurorehabilitation strategies for chronic poststroke (PS) oropharyngeal dysphagia (OD) have been mainly focused on the neurostimulation of the pharyngeal motor cortex with only marginal effects. In contrast, treatments targeting the PS oropharyngeal sensory pathway dysfunction offer very promising results, but there is little knowledge on the underlying mechanisms. We aimed to explore the neurophysiological mechanisms behind the effect of three sensory neurostimulation strategies.

Methods: We carried out a randomized two-blinded parallel group's crossover sham-controlled clinical trial in 36 patients with unilateral stroke and chronic unsafe swallow to investigate the effect of repetitive transcranial magnetic stimulation (rTMS) of the primary sensory cortex (A), oral capsaicin (B) and intra-pharyngeal electrical stimulation (IPES; C). The effect was evaluated immediately after the interventions with videofluoroscopy (VFS) and motor/sensory evoked potentials (MEP/SEP).

Key Results: Interventions induced no changes in the biomechanics of the swallow response during VFS. However, an enhancement of motor cortex excitability (latency shortening and increased size of thenar MEP) was found with active interventions (A + B + C, and B/C alone; P < .05 for all) but not with sham. Active but not sham interventions shortened pharyngeal SEP latency in the ipsilesional hemisphere (A + B + C: P2-peak, P = .039; A: N2-peak, P = .034) and antagonized the physiological habituation in pharyngeal MEP (A + B + C and A alone, P < .05 for both).

Conclusions and Inferences: Sensory pathway neurostimulation strategies caused immediate enhancement of motor cortex excitability with peripheral strategies (capsaicin and IPES) and of pharyngeal sensory conduction with rTMS. These changes support the use of sensory neurorehabilitation strategies in promoting swallow recovery in chronic PS-OD.
KEYWORDS
brain stimulation, capsaicin, evoked potentials, oropharyngeal dysphagia, stroke

1 | INTRODUCTION

Oropharyngeal dysphagia (OD) is a highly prevalent poststroke (PS) complication that impacts patients’ quality of life and morbimortality and with high socioeconomic costs. Current PS-OD management is mainly based on compensatory strategies with poor compliance and marginal improvements in swallow function. Control of swallowing depends on an extended brain network in the cortex and subcortex including at least three types of components: efferent/motor pathways, afferent/sensorial pathways, and sensorimotor connection circuits. It is commonly accepted that PS-OD is associated with the focal stroke lesion strategically positioned in the dominant swallowing cortex from which the motor pathway arises. Since early-stage “spontaneous” PS-OD recovery depends on the neuroplastic capacity of the contralesional non-dominant hemisphere to take command of the uncontrolled swallowing musculature, the inability to trigger those mechanisms might be related to a state of global cortical hypoexcitability secondary to previous or chronic lesions. On the other hand, defective conduction and integration of sensory inputs carried through the sensory swallowing pathway is a prevalent finding in chronic PS-OD, as an additional mechanism contributing to OD.

Standard PS-OD treatment is based on adaptive measures in order to avoid pulmonary aspirations. However, no therapies aiming at restoring swallow function on a neuronal level have been satisfactorily established as yet. In recent years, the neurorehabilitation strategy has focused on central activation of the motor cortex through non-invasive brain stimulation (NIBS) but although there are good results, evidence is weak. One recent randomized controlled trial (RCT) using contralesional tDfCS in acute PS-OD showed that functional recovery of swallowing was accompanied by increased activation of the swallowing network in the stimulated hemisphere supporting neuronal reorganization as the leading mechanism to achieve faster rehabilitation. Approaches to improve swallow function currently under research have shown promising results in older and PS patients with OD and include the activation of the sensory pathway through peripheral transcutaneous or intra-pharyngeal electrical stimulation (IPES) or chemically with transient receptor potential (TRP) oral agents. IPES has been found specifically valuable to treat severely affected tracheostomized PS-OD patients by increasing the proportion of patients who were ready for decannulation. Capsaicinoids have shown immediate biomechanical improvements using a high single dose while lower multiple doses have also shown sensory conduction improvements. However, no central sensory strategy in this direction has been developed as far as we know.

In this randomized, crossover, two-blinded, clinical trial, we investigated the immediate effect on chronic PS-OD of three strategies targeted to the "sensory" pathway: one "central" strategy, repetitive transcranial magnetic stimulation (rTMS) of the primary sensory cortex (SI), and two "peripheral" strategies, oral capsaicin (OC) and IPES. Specifically, we aimed to explore the potential mechanism of action of these strategies. Based on the global cortical hypoexcitability state, the lack of motor swallowing dominance and the sensory swallowing impairment these patients commonly show, we hypothesized that active treatment of the sensory swallowing pathway would induce improvements in biomechanical measures of the oropharyngeal motor response and in sensory and motor neurophysiological responses obtained with pharyngeal evoked potentials, in comparison with sham treatment.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients were prospectively recruited from the Dysphagia Unit of Hospital de Mataró during a 3-year period (2016-2018) and were considered eligible if they met the following criteria: adult patients with OD of more than 3 months from stroke occurrence. All participants were in a stable medical condition for at least one month prior to inclusion. Exclusion criteria included the following conditions: neurodegenerative disorders, epilepsy, alcoholism or drug dependency, brain or head trauma or surgery, structural causes of OD, pacemaker or metallic body implants, and pregnancy or lactation. First, they were screened with the volume-viscosity swallowing test (V-VST) to detect signs of unsafe swallow and then recruited when the impairment was confirmed with a videofluoroscopy study (VFS). The V-VST is a validated clinical assessment tool for dysphagia, an
effort test, that uses three different volumes (5, 10, and 20 mL) and viscosities (200, <50, and 4500 mPa·s) with a pulse oximeter to assess clinical signs of impaired efficacy (oropharyngeal residue, piece-meal deglutition) and safety of swallow (oxygen desaturation, voice change, and cough). Diagnostic sensitivity and specificity for OD are 0.94 and 0.88, respectively, and the reliability of V-VST is also high with an overall Kappa value of 0.628 (95% CI = 0.45-0.78). Unsafe swallow was defined with VFS as a Penetration-Aspiration Scale (PAS) score ≥ 2. To determine the swallow functional ability, we used the FOIS scale. It was determined based on the diet suggested by an SLP after VFS. For sample size calculation, and accepting a α = .05 and a β = .2 in a two-sided test, 12 subjects per group are necessary to recognize a statistically significant difference ≥ 1 unit in PAS between active and sham interventions (minimal improvement considered clinically relevant), assuming a SD = 1.1 and anticipating a drop-out rate of 20%. The following aspects were gathered from the medical record for demographic, clinical, and neurological description of the population: stroke risk factors, modified Rankin Scale, National Institute Health Stroke Scale, Barthel Index, Oxford Classification, and acute stroke topography. Additionally from data gathered in patients who had performed a brain MRI, we calculated the Fazekas score, a scale used to quantify the degree of subcortical and periventricular white matter lesions of chronic ischemic nature found in the brain hemispheres (a.k.a. leukoaraiosis).

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and the study protocol was approved by our hospital’s Institutional Review Board and Ethics Committee (CEIC06/15). All participants gave written informed consent. This clinical trial was registered in www.clinicaltrials.gov under the name “Sensory Neuromodulation Protocol for the Treatment of Post-stroke oropharyngeal Dysphagia” (NCT04052178).

2.2 | Experimental design and instrumental assessments

A two-blinded parallel group’s crossover sham-controlled RCT was used as experimental design (Figure 1). After recruitment, patients were randomly allocated using specific software (QuickCalcs, GraphPad Software 2016) to receive one of three therapeutic interventions. Patients were evaluated instrumentally with VFS and pharyngeal sensory (pSEP) and motor evoked potentials (pMEP) in order to characterize the biomechanics of the oropharyngeal swallow response (OSR) and the neurophysiological mechanisms involved in swallowing. This was done in baseline (time condition T0) and immediately after the intervention (T1). The VFS methodology has been described in detail previously. Since we considered more likely to find effects at the neurophysiological level, our primary outcome was to determine the effect size induced by the interventions on the neurophysiological variables, and the secondary outcome, the effects on the biomechanics of swallow.

Neurophysiological studies were carried out using standard procedures as described in previous studies. A two-ring electrode naso-pharyngeal catheter (Gaeltec Ltd) was used for electrical stimulation (pSEPs) and electromyographic recording (pMEPs), with the pair of electrodes placed in close contact with the pharyngeal wall at the middle line. Individualized sensory first-perception and tolerance thresholds to electrical pharyngeal stimulation (square pulses, 0.2 ms duration; DS7A, Digitimer) were first calculated. Stimulation parameters used for pSEPs were intensity of 75% tolerance threshold, frequency of 0.2 Hz and 200 pulses. pSEP recording was performed with electroencephalography at CP3/CP4/CPz referenced to the earlobe, with a 500 Hz sampling rate and using a 50 Hz notch (BrainAmp, Brain Products GmbH). Motor hotspots of both pharyngeal cortices and of the contralesional thenar primary motor cortex (M1) were located, and then, the resting motor threshold (RMT) was calculated using standard procedures and used as a measure of cortical excitability. MEPs were obtained with the intensity set at 120% of the RMT. For MEP, we used a frequency of stimulation not higher than 0.5 Hz.

In summary, we studied the pSEPs and pMEPs in both hemispheres (ipsilesional and contralesional) to pharyngeal electrical stimulation and TMS, respectively. pSEPs were obtained and recorded through specific software (BrainAmp, Brain Products GmbH), while focal TMS was carried out with a figure-of-eight coil (Magstim Rapid, The Magstim Company Limited). First, the MEP was obtained in the contralesional hemisphere from thenar eminence (tMEP), as a control measure of global cortical motor excitability. Then, pMEPs were obtained after stimulation of both hemispheres. Ten consecutive trials were gathered for tMEPs and pMEPs. All neurophysiological assessments were repeated in T1 in the same sequence after the application of the intervention, approximately 30-45 minutes after the T0 assessment. Finally, VFS was repeated at the end of T1 (approximately 2 hours after the T0 evaluation).

2.3 | Experimental interventions and safety

The effect of the interventions was investigated in “active” and “sham” conditions (named intervention conditions). Intervention consisted of the application of one of the following: rTMS of the contralesional S1, OC, or IPS. rTMS was applied at an intensity of 90% of the resting motor threshold (RMT) with the main coil axis arranged parallel to the sagittal plane of the skull. As there is still no standard procedure to establish the exact location of the S1 hotspot, we located the S1 hotspot 2 cm behind the primary-motor cortex (M1) hotspot in a straight para-sagittal line. In our patients (data not shown), this point lies approximately 3.0-4.0 cm lateral and 1.5-2.0 cm posterior to Cz in correspondence to the parietal area (P3/P4) of the 10-20 EEG system. By using this arrangement, we assured not to evoke either any clinical motor twitch in the contralateral side of the body or any evoked potential in the contralateral thenar eminence. rTMS consisted of the application of a 5 Hz-train
of 50 pulses over S1 during 10 seconds and repeated for a total of 5 times (total 250 pulses), with 10 seconds waiting time between
trains. A common method used for sham stimulation in clinical tri-
als protocols with rTMS, the coil was tilted 90° with respect to
the tangential plane of the skull and the protocol of stimulation
was applied using the same parameters described above. OC (10−5 M) or
placebo (potassium sorbate) were administered once in a 100 mL so-
lution. Active IPES was applied during 10 minutes by delivering trains
of electrical pulses to the pharynx at an intensity of 75% tolerance
threshold (0.2 ms of duration) and 5 Hz, and the same settings were
maintained but only for 30 seconds and then turned off for sham. All
patients, regardless of the intervention they were assigned, received
both active and sham treatments scheduled on two different single-
day visits (randomly allocated) and separated by a washing period
of one week. Patients were blind to intervention condition assignment
(received on each specific day) but not to the specific intervention
received. Treatment assignment was known to the researchers who
applied the intervention but data analysts were blind to patient's
condition and treatment assignment.

We monitored potential adverse events (AE) of the interventions
either during or subsequent to its application up to 3 months from
the intervention. The AE were graded according to the NCI Common
Terminology Criteria for Adverse Events v5.0 of the National
Institute of Health and then correlated with the intervention in cat-
egories according to the Causality Criteria from the World Health
Organization and the Uppsala Monitoring Centre.

2.4 Data reduction and analysis

Data analyses were performed by authors blind to the intervention
condition, time condition, and intervention type. First, we gathered
the absolute values for each parameter. From VFS, we measured the
time from glossopalatal junction (GPJ) opening (time value 0) to laryn-
geal vestibule closure (LVC) and opening (LVO) and to upper esopha-
geal sphincter opening (UESO), the final bolus kinetic energy (KE),
the propulsion force, and the mean velocity of the bolus transit (GPJ to
UESO).31 Regarding neurophysiological measures, data were obtained

FIGURE 1 Flowchart of the study. IPES, intrapharyngeal electrical stimulation; rTMS, repetitive transcranial magnetic stimulation; VFS, videofluoroscopy; V-VST, volume-viscosity swallow test
and analyzed separately by hemispheres. We measured the onset latency, the duration, the peak-to-peak amplitude, and the area under the curve of MEPs. Two types of measures were obtained: the mean value by averaging the absolute values of all trials (data not shown) and the best response by selecting the largest MEP of all trials. For the final analysis, as a well-known previously reported methodology, we used the largest MEP because it represents the maximum output capacity (i.e., excitability measurement) available in the motor pathway. We measured the peak latency and the peak-to-peak amplitude of pSEP components (N1, P1, N2, P2). The following outcome measures were obtained for each patient after data analysis: the LVC/LVO times, the UESO time, the KE, the propulsion force, and the mean velocity from the VFS; the RMT, the onset latency, the duration, the peak-to-peak amplitude and the area for each hemisphere for pMEPs and for the contralesional hemisphere for tMEPs from TMS, and the peak latencies and the peak-to-peak amplitudes for each hemisphere from pSEPs. Additionally, we obtained the higher PAS, the prevalence of unsafe swallow (PAS ≥ 2) and of oropharyngeal residue (vallecular and in pyriform sinus) by patient.

2.5 | Statistical analysis

In order to compare the magnitude of the effect induced by the intervention in a quantitative manner, we calculated the percentage change of the value obtained in T1 with respect to that of T0 (the difference between T1 and T0, divided by the value in T0, and then multiplied by 100). We thus determined the significance of the effect of the interventions (overall and by intervention type) by comparing the outcome measures between T1 and T0 as absolute values, and we also determined the magnitude of the effect by comparing the percentage change related to the intervention condition and separately by intervention type. Data were analyzed both separately by intervention and with all the interventions grouped together (rTMS + OC + IPES).

Statistical analysis was performed using GraphPad Prism 6.01. Qualitative data were analyzed by the Fisher exact test or chi-squared test for multiple comparisons. Continuous data were presented as mean ± SD and compared with the non-parametric Mann-Whitney U test or Kruskal-Wallis test for multiple comparisons with Dunn’s post-test or with the parametric t test or one-way ANOVA for multiple comparisons with Bonferroni’s post-test. To assess normality, we used the D’Agostino and Pearson omnibus normality test. Pearson’s test or Spearman’s test was used for correlation analyses. Statistical significance was set at P < .05.

3 | RESULTS

3.1 | Participants

Demographics and clinical and neurological characterization of the thirty-six patients finally included in the study are detailed in Figure 1 and Table 1. Study population consisted mostly of older mildly disabled men at risk of malnutrition, able to be orally fed and with reduced functional capacity for daily-living activities. No significant differences were found between intervention groups, except for a shorter time from stroke in patients of the capsaicin group (ANOVA, P = .013, post hoc P < .01 in comparison with IPES). Stroke was in the majority ischemic PACI-type and of left supratentorial localization. Leukoaraiosis was found in all examined patients with MRI which was moderate and affected subcortical and periventricular regions.

3.2 | Swallow biomechanical effects

In T0, patients showed high prevalence of impaired safety and efficacy of swallow, with significant delays in the LVC and UESO times. The severity of the swallow impairment in T0 was not significantly different among study groups. No specific effects on PAS and biomechanical parameters were found with the application of any intervention, either in the global analysis or separately by study group (Table 2).

3.3 | Neurophysiological effects

Neurophysiological effects (and statistically significant values) of the interventions are shown in Tables 3–5, and Figure 2 and Figure S1. The percentage change of outcome measures is represented in Figure 3. There were no significant differences in thenary and pharyngeal RMTs between T0 and T1 with active or sham interventions (data not shown for isolated analysis by intervention). Overall analysis of all interventions grouped together showed that active but not sham intervention was significantly associated with latency shortening, increased amplitude, and area of the tMEP in the contralesional hemisphere (Table 3).

Independent analysis by intervention showed significant effects of active treatment on the shortening of the tMEP latency exclusively with OC and on increased amplitude and area of the tMEP with both OC and IPES, while no effect was associated with sham interventions (Table 4, Figure 2, and Figure S1). Sham but no active condition significantly associated with reduction of pMEP duration on both hemispheres for both overall and rTMS analyses (Tables 3 and 4, Figure S1). These findings were confirmed by the fact that the percentage change of pMEP duration was significantly larger with sham than with active intervention on the ipsilesional side for grouped interventions and rTMS alone (Figure 3), suggesting that the expected physiological pMEP decay or habituation was avoided with active treatments. One-way ANOVA did not show any significant difference in the magnitude of the effect (the percentage change) between active interventions.

No significant differences were found in sensory thresholds between T0 and T1 with active or sham interventions (data not shown for isolated analysis by intervention). No significant effect was found on pSEPs in overall analyses (Table 5). Active rTMS but
# TABLE 1  Demographical, clinical, and neuroimaging characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>rTMS</th>
<th>Capsaicin</th>
<th>IPES</th>
<th>( P ) value</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td></td>
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<tr>
<td>Age</td>
<td>71.5 ± 10.3</td>
<td>70.0 ± 8.6</td>
<td>74.3 ± 7.8</td>
<td>70.0 ± 14.2</td>
<td>.532</td>
</tr>
<tr>
<td>Gender, n ♂ (%)</td>
<td>11 (29.7)</td>
<td>3 (25.0)</td>
<td>5 (41.7)</td>
<td>1 (8.3)</td>
<td>.169</td>
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<tr>
<td>Hospitalization time (d)</td>
<td>14.9 ± 14.8</td>
<td>13.5 ± 9.6</td>
<td>10.8 ± 6.8</td>
<td>18.9 ± 21.1</td>
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<tr>
<td>Time from stroke (d)</td>
<td>399.1 ± 469.9</td>
<td>493.1 ± 672.4</td>
<td>219.0 ± 309.8*</td>
<td>485.2 ± 318.3</td>
<td>.013</td>
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<td>Barthel index</td>
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<tr>
<td>At discharge</td>
<td>56.1 ± 23.3</td>
<td>45.0 ± 19.2</td>
<td>65.0 ± 30.0</td>
<td>65.0 ± 14.1</td>
<td>.374</td>
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<td>Current status</td>
<td>80.4 ± 22.3</td>
<td>79.6 ± 19.9</td>
<td>74.2 ± 27.8</td>
<td>86.9 ± 18.2</td>
<td>.477</td>
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<td>MNA-sf current status, n (%)</td>
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<td>Well-nourished</td>
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<td>1 (9.0)</td>
<td>2 (16.7)</td>
<td>1 (8.3)</td>
<td>.817</td>
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<td>6 (50.0)</td>
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</tr>
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<td>Malnourished</td>
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<td>6 (54.5)</td>
<td>4 (33.3)</td>
<td>7 (58.3)</td>
<td></td>
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<td>FOIS scale, n (%)</td>
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<tr>
<td>1</td>
<td>1 (2.8)</td>
<td>1 (8.3)</td>
<td>0</td>
<td>0</td>
<td>.534</td>
</tr>
<tr>
<td>4</td>
<td>6 (16.7)</td>
<td>1 (8.3)</td>
<td>3 (25.0)</td>
<td>2 (16.7)</td>
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</tr>
<tr>
<td>5</td>
<td>28 (77.8)</td>
<td>10 (83.3)</td>
<td>9 (75.0)</td>
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<td>6</td>
<td>1 (2.8)</td>
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<td>0</td>
<td>1 (8.3)</td>
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<td>Modified Rankin scale</td>
<td></td>
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<td>Prior to stroke</td>
<td>0.8 ± 1.3</td>
<td>1.4 ± 1.6</td>
<td>0.6 ± 1.1</td>
<td>0.4 ± 1.1</td>
<td>.238</td>
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<td>At discharge</td>
<td>3.5 ± 1.1</td>
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<td>3.6 ± 1.2</td>
<td>3.4 ± 1.1</td>
<td>.913</td>
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<td>2.3 ± 1.2</td>
<td>.411</td>
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<td>NIHSS median (IQ range)</td>
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<tr>
<td>Stroke onset</td>
<td>8.0 (4.0-14.0)</td>
<td>7.0 (3.5-10.0)</td>
<td>10.5 (3.8-17.8)</td>
<td>7.5 (3.3-14.0)</td>
<td>.542</td>
</tr>
<tr>
<td>At discharge</td>
<td>3.0 (2.0-7.0)</td>
<td>2.0 (1.0-6.0)</td>
<td>3.5 (1.0-13.3)</td>
<td>7.0 (3.0-9.0)</td>
<td>.125</td>
</tr>
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<td>Current status</td>
<td>2.0 (1.0-4.0)</td>
<td>3.5 (2.8-4.3)</td>
<td>2.0 (0.3-5.5)</td>
<td>3.0 (2.0-4.0)</td>
<td>.530</td>
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<tr>
<td>Stroke characteristics, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left side</td>
<td>24 (66.7)</td>
<td>6 (50.0)</td>
<td>9 (75.0)</td>
<td>9 (75.0)</td>
<td>.325</td>
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<td>Ischemic</td>
<td>32 (88.9)</td>
<td>12 (100.0)</td>
<td>11 (91.7)</td>
<td>9 (75.0)</td>
<td>.140</td>
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<td>Hemorrhagic</td>
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<td>1 (8.3)</td>
<td>3 (25.0)</td>
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<td>Supratentorial</td>
<td>28 (77.8)</td>
<td>8 (66.7)</td>
<td>11 (91.7)</td>
<td>9 (75.0)</td>
<td>.645</td>
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<tr>
<td>Infratentorial</td>
<td>6 (16.7)</td>
<td>3 (25)</td>
<td>1 (8.3)</td>
<td>2 (16.7)</td>
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<tr>
<td>Supra + Infratentorial</td>
<td>2 (5.6)</td>
<td>1 (8.3)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td></td>
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<tr>
<td>Oxford classification, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TACI</td>
<td>2 (6.3)</td>
<td>0 (0.0)</td>
<td>2 (100.0)</td>
<td>0 (0.0)</td>
<td>.381</td>
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<tr>
<td>PACI</td>
<td>17 (53.1)</td>
<td>7 (58.3)</td>
<td>5 (55.6)</td>
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<td>LACI</td>
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<td>2 (22.2)</td>
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<td>POCI</td>
<td>8 (25.0)</td>
<td>4 (33.3)</td>
<td>1 (11.1)</td>
<td>3 (33.3)</td>
<td></td>
</tr>
<tr>
<td>PACI + POCI</td>
<td>2 (6.3)</td>
<td>1 (8.3)</td>
<td>1 (11.1)</td>
<td>0 (0.0)</td>
<td></td>
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<tr>
<td>Fazekas grade (n = 23)</td>
<td>3.0 ± 1.5</td>
<td>3.3 ± 1.5 (n = 9)</td>
<td>2.6 ± 1.5 (n = 7)</td>
<td>3.0 ± 1.6 (n = 7)</td>
<td>.617</td>
</tr>
</tbody>
</table>

Note: Fazekas grade: 0, no alteration; 1-2, mild; 3-4, moderate; and 5-6, severe. Data values are presented as mean ± standard deviation.

Abbreviations: FOIS, Functional Oral Intake Scale (1: no oral intake; 4: total oral intake of a single consistency; 5: total oral intake of multiple consistencies; 6: total oral intake with no special preparation with restrictions); IQ, interquartile; LACI, lacunar circulation infarct; MNA-sf, Mini Nutritional Assessment short form; n, number; NIHSS, National Institute of Health Stroke Scale; PACI, partial anterior circulation infarct; PES, intrapharyngeal electrical stimulation group; POCI, posterior circulation infarct; rTMS, repetitive transcranial stimulation group; TACI, total anterior circulation infarct.

*\( P < .01 \) vs IPES.

Bold means that the statistical comparison is significant (\( P < .05 \)).
not sham induced a barely significant N2-peak latency shortening in the ipsilesional hemisphere ($P = .049$), represented by a change from $213.4 \pm 46.8$ to $188.0 \pm 50.9$ ms (Table S2). The percentage change of the P2-peak latency was significantly larger with active interventions with respect to sham in the ipsilesional hemisphere ($P = .039$; Figure 3). One-way ANOVA showed a significant difference in the
magnitude of the change of the N2-peak latency between active interventions ($F[2, 30] = 4.108, P = .026$) determined by the finding of a larger latency shortening with rTMS in comparison with IPES (Tukey’s multiple comparisons test, $P = .034$). No other significant differences were found on pSEPs parameters.

### TABLE 3  Overall effect of pharyngeal sensory pathway stimulation strategies over motor pathway outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Ipsilesional</th>
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<td>T1</td>
<td></td>
<td>T0</td>
<td>T1</td>
<td></td>
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<tr>
<td>Pharyngeal RMT (%)</td>
<td>88.4 ± 13.2</td>
<td>87.2 ± 11.9</td>
<td>.339</td>
<td>84.7 ± 13.8</td>
<td>83.2 ± 13.4</td>
<td>.860</td>
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<tr>
<td>Pharyngeal MEP</td>
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</tr>
<tr>
<td>Latency (ms)</td>
<td>8.2 ± 2.2</td>
<td>7.5 ± 1.6</td>
<td>.038</td>
<td>7.7 ± 1.4</td>
<td>7.6 ± 1.5</td>
<td>.806</td>
</tr>
<tr>
<td>Duration (ms)</td>
<td>13.8 ± 7.8</td>
<td>9.4 ± 3.2</td>
<td>.001</td>
<td>15.7 ± 7.8</td>
<td>12.3 ± 4.7</td>
<td>.009</td>
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<tr>
<td>Amplitude (mV)</td>
<td>0.043 ± 0.031</td>
<td>0.045 ± 0.030</td>
<td>.966</td>
<td>0.053 ± 0.043</td>
<td>0.059 ± 0.043</td>
<td>.215</td>
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<tr>
<td>AUC (µV/sec)</td>
<td>0.170 ± 0.150</td>
<td>0.150 ± 0.110</td>
<td>.679</td>
<td>0.221 ± 0.229</td>
<td>0.199 ± 0.140</td>
<td>.595</td>
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<tr>
<td>Thenar RMT (%)</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
<td>66.5 ± 10.5</td>
<td>66.9 ± 10.6</td>
<td>.237</td>
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<td>Thenar MEP</td>
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<td>Latency (ms)</td>
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<td>22.4 ± 1.9</td>
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<td>Duration (ms)</td>
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<td>31.0 ± 7.2</td>
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<td>Amplitude (mV)</td>
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<td>0.744 ± 0.560</td>
<td>0.722 ± 0.684</td>
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<td>AUC (µV/sec)</td>
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<td>n.a.</td>
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<td>3.010 ± 2.810</td>
<td>3.040 ± 3.210</td>
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<td>Active</td>
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<td>Pharyngeal RMT (%)</td>
<td>85.5 ± 13.0</td>
<td>84.8 ± 13.9</td>
<td>.832</td>
<td>85.5 ± 12.4</td>
<td>85.5 ± 12.8</td>
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<td>Pharyngeal MEP</td>
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<tr>
<td>Latency (ms)</td>
<td>7.7 ± 1.3</td>
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<td>7.7 ± 1.5</td>
<td>7.3 ± 1.4</td>
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<td>Duration (ms)</td>
<td>10.5 ± 5.8</td>
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<td>.373</td>
<td>13.3 ± 5.9</td>
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<td>Amplitude (mV)</td>
<td>0.040 ± 0.034</td>
<td>0.039 ± 0.030</td>
<td>.646</td>
<td>0.064 ± 0.059</td>
<td>0.065 ± 0.062</td>
<td>.393</td>
</tr>
<tr>
<td>AUC (µV/sec)</td>
<td>0.151 ± 0.151</td>
<td>0.126 ± 0.105</td>
<td>.864</td>
<td>0.252 ± 0.264</td>
<td>0.204 ± 0.216</td>
<td>.798</td>
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<tr>
<td>Thenar RMT (%)</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
<td>68.9 ± 13.3</td>
<td>70.3 ± 11.7</td>
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<tr>
<td>Thenar MEP</td>
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<tr>
<td>Latency (ms)</td>
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<td>n.a.</td>
<td></td>
<td>22.2 ± 2.1</td>
<td>21.5 ± 1.5</td>
<td>.007</td>
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<tr>
<td>Duration (ms)</td>
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<td>n.a.</td>
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<td>29.3 ± 6.2</td>
<td>30.6 ± 5.8</td>
<td>.365</td>
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<tr>
<td>Amplitude (mV)</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
<td>0.682 ± 0.483</td>
<td>0.910 ± 0.622</td>
<td>.013</td>
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<tr>
<td>AUC (µV/sec)</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
<td>2.600 ± 1.740</td>
<td>3.800 ± 2.830</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: Data values are presented as mean ± standard deviation. Abbreviations: %, percentage; µV/sec, microvolts per second; AUC, area under the curve; MEP, motor evoked potential; ms, milliseconds; mV, millivolts; n.a., not applicable; RMT, resting motor threshold; T0, baseline assessment; T1, postintervention assessment. Bold means that the statistical comparison is significant ($P < .05$).

### 3.4 | Adverse events

No seizures were induced with any intervention. One patient presented syncope during active rTMS application that fully recovered after a few minutes (AE severity: grade 2; causality AE category: possible). He was excluded from further analysis because of incomplete assessment. Five patients complained of pharyngeal discomfort during the first minutes of IPES which was tolerable (AE: grade 1; certain) and did not prevent continuing the intervention in three of them (Figure 1).

### 4 | DISCUSSION

This study performed on chronic PS-OD patients provides neurophysiological evidence that sensory neurorehabilitation strategies can rapidly induce functional changes in both motor and sensory pathways/circuits involved in swallowing. While peripheral oropharyngeal pharmacological and electrical sensory stimulation enhanced global motor excitability, direct central sensory-cortex stimulation increased pharyngeal sensory conduction. OC was the strategy that induced the largest changes. The effects were found at neurophysiological level and may not necessarily be extrapolated to
clinical outcomes. The changes we observed in neurophysiological measures of the swallow pathway could be the mechanisms underlying the therapeutic effect of more "chronic" sensory stimulation strategies as seen in older patients with chronic OD.¹⁷,¹⁹

Oropharyngeal dysphagia is a major and prevalent complication in the chronic PS phase.² Stroke lesions may affect any structure/pathway in the brain so the spectrum of the neurological phenotype is broad and will depend directly on the specific pathway affected. Thus, different mechanisms (either motor, sensory, or both) may co-exist in variable proportions to contribute to the final phenotype and severity in PS-OD patients.⁵,⁷,⁸ A high degree of heterogeneity in these aspects may explain the lack of strong evidence found in the search of effective rehabilitation strategies.

### 4.1 Central neurostimulation strategies

Non-invasive brain stimulation have been used to promote recovery of neurological disability.³³ Promising results in the treatment of PS-OD have been found although still not strong enough to support clinical applicability.⁹,¹⁰ NIBS paradigms differ in targeted hemisphere (ipsilesional, contralesional, or bihemispheric), neurophysiological mechanisms (excitation or inhibition), stimulation parameters, and timing of application (acute, subacute, or chronic phase), among others aspects. RCTs are highly variable regarding the primary endpoints evaluated (assessed by clinical and instrumental methods) and provide different measures of the OSR. A few studies summarize the current and limited evidence

### TABLE 4 Effect of each pharyngeal sensory pathway stimulation strategy (active intervention) on motor evoked potentials

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<td>T1</td>
<td>P value</td>
<td>T0</td>
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<td>rTMS pMPE latency (ms)</td>
<td>7.8 ± 1.6</td>
<td>7.2 ± 2.0</td>
<td>.479</td>
<td>7.5 ± 1.8</td>
</tr>
<tr>
<td>rTMS pMPE duration (ms)</td>
<td>11.4 ± 5.9</td>
<td>11.1 ± 4.3</td>
<td>.717</td>
<td>13.0 ± 7.5</td>
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<tr>
<td>rTMS pMPE amplitude (mV)</td>
<td>0.042 ± 0.031</td>
<td>0.038 ± 0.018</td>
<td>.589</td>
<td>0.058 ± 0.036</td>
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<tr>
<td>rTMS pMPE AUC (µVsec)</td>
<td>0.176 ± 0.191</td>
<td>0.138 ± 0.103</td>
<td>.900</td>
<td>0.200 ± 0.135</td>
</tr>
<tr>
<td>tMPE latency (ms)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>21.4 ± 1.7</td>
</tr>
<tr>
<td>tMPE duration (ms)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>29.1 ± 8.1</td>
</tr>
<tr>
<td>tMPE amplitude (mV)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.886 ± 0.637</td>
</tr>
<tr>
<td>tMPE AUC (µVsec)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>3.090 ± 2.222</td>
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<tbody>
<tr>
<td>Capsaicin pMPE latency (ms)</td>
<td>7.4 ± 1.2</td>
<td>6.9 ± 1.6</td>
<td>.216</td>
<td>7.8 ± 1.7</td>
<td>7.3 ± 1.4</td>
<td>.263</td>
</tr>
<tr>
<td>Capsaicin pMPE duration (ms)</td>
<td>9.9 ± 6.2</td>
<td>8.1 ± 2.4</td>
<td>.414</td>
<td>11.9 ± 4.5</td>
<td>9.4 ± 2.5</td>
<td>.056</td>
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<tr>
<td>Capsaicin pMPE amplitude (mV)</td>
<td>0.034 ± 0.030</td>
<td>0.033 ± 0.019</td>
<td>.935</td>
<td>0.046 ± 0.062</td>
<td>0.031 ± 0.022</td>
<td>.652</td>
</tr>
<tr>
<td>Capsaicin pMPE AUC (µVsec)</td>
<td>0.120 ± 0.147</td>
<td>0.103 ± 0.071</td>
<td>.633</td>
<td>0.219 ± 0.355</td>
<td>0.110 ± 0.133</td>
<td>.758</td>
</tr>
<tr>
<td>Capsaicin tMPE latency (ms)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>22.3 ± 1.7</td>
<td>21.0 ± 1.4</td>
<td>.022</td>
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<tr>
<td>Capsaicin tMPE duration (ms)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>27.4 ± 5.3</td>
<td>31.8 ± 8.6</td>
<td>.092</td>
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<tr>
<td>Capsaicin tMPE amplitude (mV)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.465 ± 0.339</td>
<td>1.000 ± 0.970</td>
<td>.018</td>
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<tr>
<td>Capsaicin tMPE AUC (µVsec)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>1.820 ± 1.393</td>
<td>4.100 ± 4.440</td>
<td>.009</td>
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<tbody>
<tr>
<td>IPES pMPE latency (ms)</td>
<td>7.9 ± 1.0</td>
<td>8.1 ± 1.1</td>
<td>.688</td>
<td>7.8 ± 0.7</td>
<td>7.5 ± 0.9</td>
<td>.508</td>
</tr>
<tr>
<td>IPES pMPE duration (ms)</td>
<td>10.1 ± 5.9</td>
<td>8.8 ± 5.4</td>
<td>.479</td>
<td>15.1 ± 5.5</td>
<td>13.9 ± 4.7</td>
<td>.938</td>
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<td>IPES pMPE amplitude (mV)</td>
<td>0.043 ± 0.042</td>
<td>0.044 ± 0.047</td>
<td>.945</td>
<td>0.091 ± 0.069</td>
<td>0.094 ± 0.073</td>
<td>.820</td>
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<tr>
<td>IPES pMPE AUC (µVsec)</td>
<td>0.160 ± 0.120</td>
<td>0.132 ± 0.134</td>
<td>.461</td>
<td>0.343 ± 0.254</td>
<td>0.260 ± 0.230</td>
<td>.698</td>
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<td>IPES tMPE latency (ms)</td>
<td>n.a.</td>
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<td>n.a.</td>
<td>23.0 ± 2.4</td>
<td>22.3 ± 1.8</td>
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<td>IPES tMPE duration (ms)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>31.5 ± 3.7</td>
<td>30.7 ± 4.1</td>
<td>.572</td>
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<tr>
<td>IPES tMPE amplitude (mV)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.676 ± 0.359</td>
<td>0.809 ± 0.314</td>
<td>.026</td>
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<tr>
<td>IPES tMPE AUC (µVsec)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>2.780 ± 1.390</td>
<td>3.550 ± 1.400</td>
<td>.043</td>
</tr>
</tbody>
</table>

Note: Data values are presented as mean ± standard deviation.
Abbreviations: µVsec, microvolts per second; AUC, area under the curve; IPES, intrapharyngeal electrical stimulation; ms, milliseconds; mV, millivolts; n.a., not applicable; pMPE, pharyngeal motor evoked potential; rTMS, repetitive transcranial magnetic stimulation; T0, baseline assessment; T1, postintervention assessment; tMPE, thenar motor evoked potential.
Bold means that the statistical comparison is significant (P < .05).

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CABIB ET AL.
In general terms, pharyngeal M1-rTMS, mainly in the contralesional hemisphere, is the most effective neurostimulation strategy to promote clinical recovery, with positive results pointing tentatively toward "excitation" rather than "inhibition" for a better outcome, although this last issue is still under discussion. However there are no studies assessing the effect of tTMS on the sensory cortex (S1) for the treatment of OD as we have evaluated in this paper. On the other hand, the effects after transcranial direct current stimulation protocols in PS-OD are of lesser magnitude and commonly need peripheral paired co-activation.

In contrast, in this study we focused only on chronic PS-OD patients, a population with worse recovery prognosis in response to neurorehabilitation, probably due to a chronic hypoexcitability state with reduced capacity to trigger neuroplastic reorganizational phenomena. This fact, in addition to the one that we only explored the immediate neurophysiological effect of the interventions, could explain the absence of OSR improvement. We used the contralesional high-frequency approach, although less investigated, in order to promote compensatory functional recovery from the unaffected hemisphere. A previous study using this approach in a 2-week regimen showed a reduction of the prevalence of aspirations and pharyngeal residue. This approach shows lower risk of seizures than the ipsilesional high-frequency approach (as we did not have any case) and could lead to greater long-term effects (especially if applied early) because of the higher reorganizational capacity of a non-damaged neuron tissue.

Randomized controlled trials in PS-OD have focused on M1 activation as the primary target to induce swallow recovery. Control of any motor task requires appropriate sensory-motor coupling, and therefore, an impairment of any of the parts of the circuit could lead to a neurological dysfunction, such as OD. Because of the afferent pathway impairment commonly found in PS-OD patients, we investigated the rTMS effect by targeting the S1 as a novel variation of the approach. Very few studies have investigated the effect of NIBS targeting sensory structures of the brain. The 10-20 EEG system is a reliable low-cost method to reach desired cortical regions to be applied in neuroscience research protocols. We combined the

### TABLE 5 Overall effect of the sensory pathway stimulation strategies on the pharyngeal sensory evoked potentials (SEP)

<table>
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<tr>
<th></th>
<th>Ipsilesional</th>
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<th>P value</th>
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<td>T1</td>
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<td>First perception</td>
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<td>9.6 ± 5.3</td>
<td>.447</td>
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<td>9.6 ± 5.3</td>
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<td>Tolerance</td>
<td>21.7 ± 10.1</td>
<td>21.1 ± 9.7</td>
<td>.613</td>
<td>21.7 ± 10.1</td>
<td>21.1 ± 9.7</td>
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<td>Pharyngeal SEP</td>
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<td>N1 latency (ms)</td>
<td>87.1 ± 25.3</td>
<td>82.3 ± 21.4</td>
<td>.465</td>
<td>79.8 ± 17.7</td>
<td>77.1 ± 22.6</td>
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<td>P1 latency (ms)</td>
<td>133.8 ± 37.1</td>
<td>128.2 ± 31.3</td>
<td>.387</td>
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<td>N2 latency (ms)</td>
<td>196.8 ± 45.4</td>
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<td>184.5 ± 33.6</td>
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<tr>
<td>P2 latency (ms)</td>
<td>254.2 ± 52.3</td>
<td>257.7 ± 41.1</td>
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<td>237.4 ± 40.5</td>
<td>243.6 ± 40.6</td>
<td>.681</td>
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<td>N1-P1 amplitude (µV)</td>
<td>2.5 ± 4.8</td>
<td>2.4 ± 3.9</td>
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<td>1.9 ± 1.7</td>
<td>.116</td>
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<td>P1-N2 amplitude (µV)</td>
<td>1.8 ± 2.7</td>
<td>2.4 ± 3.8</td>
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<td>1.2 ± 1.0</td>
<td>1.9 ± 1.9</td>
<td>.238</td>
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<tr>
<td>N2-P2 amplitude (µV)</td>
<td>1.6 ± 1.6</td>
<td>2.6 ± 4.9</td>
<td>.352</td>
<td>1.2 ± 0.9</td>
<td>1.5 ± 1.6</td>
<td>.930</td>
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**Active**

<table>
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<th>Ipsilesional</th>
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<th>P value</th>
<th>Contralesional</th>
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<tr>
<td></td>
<td>T0</td>
<td>T1</td>
<td></td>
<td>T0</td>
<td>T1</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal threshold (mA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First perception</td>
<td>11.0 ± 6.4</td>
<td>10.8 ± 6.7</td>
<td>.489</td>
<td>11.0 ± 6.4</td>
<td>10.8 ± 6.7</td>
<td>.489</td>
</tr>
<tr>
<td>Tolerance</td>
<td>24.4 ± 10.4</td>
<td>23.6 ± 10.9</td>
<td>.545</td>
<td>24.4 ± 10.4</td>
<td>23.6 ± 10.9</td>
<td>.545</td>
</tr>
<tr>
<td>Pharyngeal SEP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1 latency (ms)</td>
<td>85.1 ± 18.2</td>
<td>84.2 ± 22.9</td>
<td>.872</td>
<td>83.1 ± 18.5</td>
<td>80.7 ± 21.4</td>
<td>.919</td>
</tr>
<tr>
<td>P1 latency (ms)</td>
<td>141.6 ± 33.3</td>
<td>136.6 ± 36.1</td>
<td>.359</td>
<td>133.6 ± 32.5</td>
<td>127.4 ± 34.3</td>
<td>.344</td>
</tr>
<tr>
<td>N2 latency (ms)</td>
<td>208.8 ± 42.6</td>
<td>196.9 ± 44.8</td>
<td>.100</td>
<td>199.1 ± 40.4</td>
<td>191.5 ± 45.9</td>
<td>.205</td>
</tr>
<tr>
<td>P2 latency (ms)</td>
<td>263.3 ± 43.9</td>
<td>249.0 ± 44.8</td>
<td>.069</td>
<td>253.3 ± 43.9</td>
<td>250.9 ± 45.9</td>
<td>.451</td>
</tr>
<tr>
<td>N1-P1 amplitude (µV)</td>
<td>2.0 ± 2.6</td>
<td>1.7 ± 3.3</td>
<td>.509</td>
<td>1.5 ± 1.8</td>
<td>1.3 ± 1.1</td>
<td>.850</td>
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<tr>
<td>P1-N2 amplitude (µV)</td>
<td>1.9 ± 1.6</td>
<td>1.9 ± 4.1</td>
<td>.109</td>
<td>1.5 ± 1.3</td>
<td>1.5 ± 1.2</td>
<td>.858</td>
</tr>
<tr>
<td>N2-P2 amplitude (µV)</td>
<td>1.6 ± 1.9</td>
<td>1.2 ± 1.2</td>
<td>.135</td>
<td>1.5 ± 1.4</td>
<td>1.3 ± 1.4</td>
<td>.820</td>
</tr>
</tbody>
</table>

Note: Data values are presented as mean ± standard deviation.
Abbreviations: µV, microvolts; mA, milliamps; ms, milliseconds; SEP, sensory evoked potential; T0, baseline assessment; T1, post-intervention assessment.

on PS-OD. In general terms, pharyngeal M1-rTMS, mainly in the contralesional hemisphere, is the most effective neurostimulation strategy to promote clinical recovery, with positive results pointing tentatively toward "excitation" rather than "inhibition" for a better outcome, although this last issue is still under discussion. However there are no studies assessing the effect of rTMS on the sensory cortex (S1) for the treatment of OD as we have evaluated in this paper. On the other hand, the effects after transcranial direct current stimulation protocols in PS-OD are of lesser magnitude and commonly need peripheral paired co-activation.

In contrast, in this study we focused only on chronic PS-OD patients, a population with worse recovery prognosis in response to neurorehabilitation, probably due to a chronic hypoexcitability state with reduced capacity to trigger neuroplastic reorganizational phenomena. This fact, in addition to the one that we only explored the immediate neurophysiological effect of the interventions, could explain the absence of OSR improvement. We used the contralesional high-frequency approach, although less investigated, in order to promote compensatory functional recovery from the unaffected hemisphere. A previous study using this approach in a 2-week regimen showed a reduction of the prevalence of aspirations and pharyngeal residue. This approach shows lower risk of seizures than the ipsilesional high-frequency approach (as we did not have any case) and could lead to greater long-term effects (especially if applied early) because of the higher reorganizational capacity of a non-damaged neuron tissue.

Randomized controlled trials in PS-OD have focused on M1 activation as the primary target to induce swallow recovery. Control of any motor task requires appropriate sensory-motor coupling, and therefore, an impairment of any of the parts of the circuit could lead to a neurological dysfunction, such as OD. Because of the afferent pathway impairment commonly found in PS-OD patients, we investigated the rTMS effect by targeting the S1 as a novel variation of the approach. Very few studies have investigated the effect of NIBS targeting sensory structures of the brain. The 10-20 EEG system is a reliable low-cost method to reach desired cortical regions to be applied in neuroscience research protocols. We combined the
previous approach with a neurophysiological technique\textsuperscript{29}. Because S1 is closely attached to M1 in posterior direction, we assured the postrolandic localization of rTMS by moving away in a straight line back a couple of centimeers from M1 and by not evoking MEPs or motor twitch with single TMS pulses. Protocols using combined techniques such as neuronavigation and functional neuroimaging are probably more reliable but also much more expensive approaches.

Excitatory contralesional S1-rTMS induced a latency shortening on the pSEP N2-peak in the ipsilesional hemisphere and also the maintenance of cortical pharyngeal motor excitability after repeated stimulation in the contralesional hemisphere. The neurophysiological effect on pSEP found with rTMS but not with other interventions could be expected because of the larger spatial proximity of the induced rTMS-magnetic field in comparison with oropharyngeal interventions. There are no studies investigating the effect on the afferent pathway after S1-rTMS. This rTMS effect, although of small magnitude in proportion for the large time scale window of pSEPs, could be related to increase velocity conduction or integration of the sensory volleys coming from the oropharynx, but we did not find any correlation with OSR improvement. Latency shortening of pSEP has previously been correlated with improved LVC time in older OD patients after a 10-day regimen of OC,\textsuperscript{18} suggesting the effect responsible for the swallow recovery was central. Otherwise, Khedr et al\textsuperscript{34} found an increase size in esophageal MEPs of both hemispheres after ipsilesional high-frequency rTMS, suggesting an enhanced excitability effect on M1. Habituation of MEPs (ie, size reduction after repeated TMS) can be a common finding after long duration protocols, as we found in sham condition. This physiological finding was avoided in the active condition, suggesting that S1-rTMS enhances (in a relative manner with respect to sham) cortical motor excitability. Mechanisms behind this effect may lie in several structures of the brain cortex. In fact, the effects of rTMS are not determined exclusively by direct activation of the cortico-spinal tract and pyramidal neurons of the cerebral cortex but also by concomitant activation of neighboring circuitry.\textsuperscript{40} As far as we know, our study is the first RCT to demonstrate neurophysiological improvements in chronic PS-OD using contralesional high-frequency S1-rTMS.

### 4.2 Peripheral neurostimulation strategies

Strategies to recover swallow function commonly used in patients with OD, such TES and IPES, are based on electrical stimulation of oropharyngeal structures but only recently has there been stronger evidence for their clinical applicability. While sensory-intensity TES is thought to promote recovery by enhancing sensory brain inputs, motor-intensities also acts by improving muscle performance. The recent finding of contributing sensory impairments to PS-OD\textsuperscript{7} has promoted the interest to find novel strategies. A first study by our group on 20 chronic PS-OD patients found that 10-days/1-hour regimen with either sensory or motor TES significantly improved swallow biomechanics, and safety and efficacy of swallow.\textsuperscript{41} In addition, a 10-day regimen of sensory/motor TES applied on 89 PS-OD patients reduced the prevalence of impaired swallow and improved the OSR timing, with a lasting effect of 1 year.\textsuperscript{42} In fact, favorable results in PS-OD using TES have been published in the latest edition of The National Institute for Health and Care Excellence Guidelines.\textsuperscript{43}

In contrast, the evidence supporting IPES is weaker and comes mostly from pilot studies. A larger RCT performed on subacute PS-OD showed negative results in a 3-day regimen but undertreated patients probably contributed to the non-effect.\textsuperscript{44} We found that IPES induced a tMEP enhancement (although without latency
shortening as seen with OC) suggesting that its mechanism involves the brain cortex. Another study showed that IPES increases levels of substance P in saliva of healthy persons which puts this as a potential marker of the effect to be applied in future research. From our study, we gathered evidence of the central effects of IPES that could contribute to a potential recovery of OD.

In addition, some new pharmacological strategies have shown promising results including oropharyngeal stimulation with TRP agonists. On a previous comparative study capsaicinoids had a stronger effect by accelerating the OSR by stimulating TRPV1 over TRPV1/A1 or TRPM8. Another study of our group on older patients (including PS-OD) found that high doses of capsaicinoids (150 µmol/L) immediately improved the OSR and safety of swallow, although some patients complained about the pungency of the stimulant. Capsaicinoids used in lower doses (10 µmol/L), like in this present study, have also shown biomechanical and pSEP improvements (N1-peak shortening and increased P1-N2/N2-P2 amplitude) but only after multiple doses (10-days) in older patients with OD. Additionally, these authors found a correlation between shortening of pSEP latency and LVC time. In our study, we found only a slight N2-peak pSEP shortening in the ipsilesional hemisphere after rTMS. We believe that the magnitude of this result is probably related to the single treatment, lower dose, and short-term follow-up as a difference from the daily treatments regimens in other studies. In the pharyngeal mucosa epithelium, capsaicin is one of several TRP agonists that induces sensory nerve impulses. Central effect of TRPV1 agonists was also found in our study using a single high dose of OC: This showed in latency shortening and increased size of the tMEP, demonstrating that the enhancing effect over M1 was immediate. This finding adds to the more chronic effect found on the sensory pathway after repeated doses. A possible effect on sensory pathways/circuits of both OC and IPES cannot be ruled out because of the short follow-up of a one-session treatment.
4.3 | Limitations

Because we used a crossover design with a 1-week “washing out” window in between, we cannot rule out a possible carryover effect on T1 generated by the effects of the therapy applied on T0, although if this occurred equally in both arms, the effect would be canceled. However, a carryover “inhibitory” effect in those patients treated first with active and then with sham treatment (leading to longer baseline pMEP latency) could explain the unexpected shortening pMEP latency effect found after the sham intervention in the ipsilesional side, among other less unlikely explanations (as a placebo effect). Until new methodologies are encountered, we cannot discard that the effects found with rTMS over S1 are generated by co-stimulation of other nearby brain areas (including M1). A slightly shorter time after stroke was found in the group treated with OC which could allow them to respond better to interventions.

5 | CONCLUSIONS AND IMPLICATIONS

At the doses and intensities used in this study performed in chronic PS-OD, acute sensory neurorehabilitation strategies did not induce any negative effects on motor/sensory circuitry shown as an enhancement on motor cortical excitability with peripheral stimulation and, to a lesser extent, a shortening in pharyngeal sensory conduction with central stimulation. These are safe therapeutic strategies with no significant AEs. The biomechanical and clinical improvements observed with peripheral rehabilitation strategies might be associated with the central neurophysiological effects found in this study. The potential excitatory effect of TRP agonists applied to disabled neurological patients may open a new approach to recover the impairments leading to OD. Chronic PS-OD patients’ phenotype supports targeting the sensory or afferent pathway with either peripheral or central strategies in combination with the motor pathway as a novel therapeutic method that deserves to be further investigated.

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DISCLOSURE

No competing interests declared.

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REFERENCES


SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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