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Tactile, gustatory, and visual biofeedback stimuli modulate neural substrates of deglutition

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Abstract

It has been well established that swallowing kinematics are modified with different forms of exogenous and endogenous input, however the underlying neural substrates associated with these effects are largely unknown. Our objective was to determine whether the swallowing BOLD response is modulated with heightened sensory modalities (taste, cutaneous electrical stimulation, and visual biofeedback) compared to water ingestion (control) in healthy adults across the age span. Habituation and sensitization were also examined for each sensory condition. Our principal findings are that each sensory swallowing condition activated components of the swallowing cortical network, plus regions associated with the particular sensory modality (i.e. primarily frontal motor planning and integration areas with visual condition). Overall, the insula was most commonly active among the sensory modalities. We also discuss gradual increases and decreases in BOLD signal with repeated exposures for each condition. We conclude that both stimulus- and intention-based inputs have unique cortical swallowing networks relative to their modality. This scientific contribution advances our understanding of the mechanisms of normal swallowing cortical control and have the potential to impact clinical uses of these modalities in treatments for neurogenic dysphagia.

Keywords

deglutition; fMRI; taste; electrical stimulation; habituation; sensitization

Introduction

Swallowing is necessary to sustain life by allowing safe passage of food and saliva beyond the airway and into the stomach. Neural imaging studies report multiple cortical regions associated with swallowing, including the primary sensory and motor regions, insula, premotor cortex, inferior frontal gyrus and cingulate gyrus (Mosier and Bereznaya, 2001). A

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key component of normal swallowing is sensorimotor integration, wherein multiple neuromuscular events, once triggered, occur during the pharyngeal phase – they include elevation of the velum, hyoid bone and laryngeal elevation and intrinsic closure, pharyngeal squeeze, and opening of the upper esophageal sphincter (Logemann, 1988). A bolus with more salient properties than water or saliva (i.e. taste, temperature, and volume) can change the timing and extent of movement of each of these events with heightened, exogenous (stimulus-based) input. (Bisch et al., 1994; Chi-Fishman and Sonies, 2002; Ding et al., 2003). Also, cutaneous electrical stimulation on the neck administered during swallowing has been shown to improve the timing of swallowing in patients with swallowing impairment (dysphagia) (Gallas et al., 2010; Ludlow et al., 2007). Endogenous (intention-based) forms of input may also modify swallowing and are unique because they provide information about swallowing behavior and require voluntary attention to the task. Given a command or visual biofeedback (i.e. EMG, accelerometer), one can volitionally lengthen the duration of hyoid bone and laryngeal elevation with a technique called the Mendelsohn maneuver (Kahrilas et al., 1991). These effects are observed across the age-span in healthy adults (Ding et al., 2003; Hind et al., 2001), but are of particular significance in older adults, since many neurologically-based swallowing impairments are most prevalent with advancing age (i.e. stroke, Alzheimer's and Parkinson's diseases). Dysphagia treatments often involve both exogenous and endogenous techniques (Chaudhuri et al., 2002; Logemann and Kahrilas, 1990; Pelletier and Lawless, 2003). Despite evidence that swallowing kinematics can be modified with different forms of input, the underlying neural substrates associated with these effects are still largely unknown. Taste (sour bolus), cutaneous submental stimulation, and visual bio-feed back are of particular interest because they are readily employed in clinical settings and, as noted above, are shown to have immediate effects on swallowing biomechanics and might be captured with neural imaging techniques.

Specific neural networks have been identified for some stimulus-based and intention-based stimuli in other functional systems (Debaere et al., 2003; Herwig et al., 2007). There is also evidence that repeated exposures to various stimuli are associated with habituation (gradually decreasing BOLD signal or blood oxygen level dependent signal) and/or sensitization (gradually increasing BOLD signal), progressively changing the intensity of the neural response (Christmann et al., 2007; Coen et al., 2007; Wagner et al., 2006; Yousem et al., 1997). In the case of swallowing, it is unknown how both endogenous and exogenous sensory inputs alter the swallowing cortical network or whether repeated exposure to a sensory modality will gradually increase or decrease the BOLD signal in this network, when tested within the same paradigm. This is significant because treatment-based stimuli are often applied numerous times during a treatment session. The goal of this study was to examine BOLD response for swallowing during three conditions including taste, cutaneous electrical stimulation, and visual biofeedback relative to swallowing water (control) across the age-span. We also investigated changes in BOLD response with repeated exposures to the stimulus during the study. We expected that cortical regions commonly involved in swallowing (pre- and post-central gyri, insula, anterior cingulate, supplementary motor area or SMA, and inferior frontal gyrus and inferior parietal gyrus), would be modulated with all forms of sensory input. Finally, we predicted that habituation and sensitization would be evident primarily in regions associated with the respective sensory modality. If our predictions are correct, it could influence which sensory-based treatments better target particular cortical regions that have been affected and are responsible for neurogenic dysphagia.

Materials and Methods

This study involved 19 healthy adults, including nine young (mean age 25.8 (± 4.1); range 22–32 yrs) and ten old (mean age 67.3 (± 9.2); range 60–82). All participants were without swallowing, speech, or cognitive disorder, or any other chronic medical condition. Each participant provided written informed consent to participate in this study, which was approved by the Institutional Review Board of the Johns Hopkins Medical Institute.

fMRI procedures

Each participant was familiarized with the study procedures before participating. This study involved 4 runs with 80 swallows, each run with a specific condition with 20 swallows including: distilled water, sour liquid, distilled water with cutaneous electrical stimulation (e-stim), and distilled water with visual biofeedback of swallowing. All swallows were of 5ml, room-temperature liquid of the same consistency and were infused directly onto the anterior-mid region of the tongue via plastic tubing that was dispensed by a MR-safe injector (Spectris Solaris®, Medrad) (Figure 1A). Sour water and distilled water were infused with separate tubing. Participants were instructed to swallow once they felt that the liquid had completely entered their mouths. The inter-stimulus interval for all swallows was 18 seconds. To ensure task compliance, swallowing was monitored with an oral pressure system that consisted of a water-filled tube that extended from the oral cavity to a transducer, which measured fluid displacement with each swallow. This pressure transducer only detects pressure differences in the oral cavity, not pharyngeal changes and not pressure changes by pushing directly on the small tubes in the mouth as with lingual pressure devices. A wash out period followed the taste run; participants were given water boluses before subsequent runs to remove any residual sour taste on the tongue.

Swallowing conditions

The order of the four conditions was randomly assigned. The distilled water run was the control condition. The taste condition included a sour bolus (citric acid USP 0.65g/100 ml distilled water, odorless). E-stim was administered to the anterior neck with two adhesive surface electrodes (silver/silver chloride Ambu®; skin contact size 28×20 mm in diameter) located on either side of the larynx and approximately one-inch apart, as determined by palpation. E-stim was only administered during swallowing and only at a (low) sensory level. The stimulation intensity was determined by each participant, where they were instructed to indicate when the stimulation was felt (typically a prickly sensation) but without the feeling of a muscle contraction. The first author has experience with administering sensory-level and motor- or muscle-contraction-level stimulation to the skin overlying the larynx in previous experiments (Humbert et al., 2006; Ludlow et al., 2007). For the visual biofeedback condition, the signal from the oral pressure-monitoring device was displayed to the participant during swallowing. Thus, real-time monitoring of oral pressure changes (by the investigator) and presentation to the participant occurred simultaneously. Signal amplitude changes representative of actual swallowing occurred only during swallowing (Figure 1B), so the periods between swallowing in this condition displayed a flat-lined signal, unlike EMG, which can be overly sensitive to small tongue movements between swallowing events. These visual signals were viewed through a mirror that was mounted atop the head coil. For the three other runs without visual biofeedback, only a white glare was seen through the mirror, to control for effect of light separate from the oral pressure signal information. All participants agreed they could clearly see the signal without straining or adjusting the position of their heads.

Functional imaging

All MR imaging was acquired with a 3T Phillips MRI scanner, an 8-channel head coil with parallel imaging capability. Using multi-slice 2D SENSE T2* gradient-echo, echo planar imaging (EPI) pulse sequence, functional images were obtained in the axial plane. Higher order shimming was applied to the static magnetic field (B0). The EPI parameters were as follows: echo time 30 ms; repetition time (TR) = 2000 ms; flip angle = 75°; acquisition matrix =80×80 voxels; FOV=240 mm; SENSE factor of 2. This protocol acquired 37 axial brain slices per TR (3 mm thick slices with 1 mm slice gap), and a time course of 189 temporal whole brain image volumes, after discarding first five volumes to ensure steady state. Padding the head within the head coil minimized movement.

Anatomical T1 brain images were used as a template for spatial normalization of functional scans, for clinical over-reads to detect abnormalities and exclude ineligible participants. Anatomical scan parameters were performed using an 8-channel head coil, 240 cm field-of-view (FOV), and a 1-mm isotropic MP-RAGE, which takes 6 minutes with SENSE factor 2. Axial T1-weighted fspgr (TR/TE 215/12), axial diffusion-weighted (10,000/13), and axial T2-weighted frFSE w fatsat (3440/68) fast spin echo scans were obtained through the brain.

fMRI image processing

All functional images were processed with Statistical Parametric Mapping (SPM5, Wellcome Department of Imaging Neuroscience, University College London, UK). Images were slice-timing corrected, motion-corrected, normalized to the MNI template using unified segmentation of the Anatomical T1 weighted image, re-sampled to 2 mm isotropic voxels, and smoothed with 6 mm FWHM Gaussian kernel.

fMRI Statistics

First-level analyses of the time series data were performed for individual participants using a general linear model. Swallow onset times for each condition were obtained directly using the oral pressure signals. The vectors of onset for each condition were convolved with the canonical hemodynamic response function (HRF) to construct the statistical model, resulting in a 4-column design matrix. In addition, the six motion parameters obtained from motion correction was added for each session in the design matrix to account for spin history artifacts associated with motion. Time points with higher than 3 mm translational or 2 degrees rotational differential motion were removed using stick regressors. The general linear-model removed the low frequencies with a 128 s high-pass filter.

Second-level analyses contrasting between age groups and swallow type was performed using estimates of BOLD activation amplitude images for water, sour water, water plus e-stim and water plus visual biofeedback for each group. BOLD amplitude images were from first-level contrasts of each swallow type. T-contrasts were used to determine significant differences in the 3 conditions compared to control (water). All analyses were at the $p<0.001$ uncorrected threshold and only clusters with at least 70 edge-connected voxels were considered providing an effective p-value of 0.05.

We further analyzed activation using a region of interest (ROI) analysis of the swallowing network to assess differences that were not found in the whole brain analysis, including the bilateral pre- and post-central gyri (M1 and S1), insula, anterior cingulate cortex (ACC), supplementary motor area (SMA), and inferior frontal gyrus (IFG) and inferior parietal gyrus (IPG). This was based on previous studies of the swallowing cortical network (Hamdy et al., 1999; Martin et al., 2001). The insula was of interest, so we extracted the peak % signal change for each trial from the time course values and obtained the average by condition (Figure 2).

Habituation and sensitization

To determine whether there were gradual increases or decreases in signal over time, linear time modulation was used in the general linear model. The regions that are shown to be significant in habituation or sensitization are the regions that show a decreasing or increasing linear trend over the 20 activations, respectively, within a run.

Results

All participants tolerated the tasks well and completed them with 100% task compliance within each condition. In addition to many regions in the swallowing cortical network, BOLD responses were found in visual and cognitive regions that are likely associated with ongoing monitoring of the experimental setting and not necessarily with swallowing (Supplementary Table). Therefore, the following results and discussion will focus primarily on findings within the swallowing cortical network. A few regions commonly associated with swallowing (i.e. precentral gyrus) were active in clusters that included fewer than 70 edge-connected voxels (between 23 and 68; noted in Table 1). Because swallowing can be challenging to image due to associated motion and since we are interested in the swallowing regions alone, we will also discuss these regions with a slightly higher false positive rate. The young and old comparisons yielded few cortical regions and can be viewed in the Supplemental Table.

Main Effects (Table 1)

For the water condition, M1, S1, ACC, IFG opercularis, and IPG were active. In sour swallows, S1, ACC, insula, SMA, IFG opecularis and triangularis, and IPG were active. The visual condition was associated with activity in ACC, insula, SMA, IFG opercularis and triangularis, IPG, and the Rolandic operculum. The e-stim condition had the least activity, including M1 and the insula. Figure 2 differentiates the left and right as well as the anterior and posterior insula across conditions. These data show greater activation in the right, anterior insula for the three sensory conditions compared to the water condition, which had somewhat more signal in the left insula and balanced between anterior and posterior regions.

Condition contrasts (Table 1)

BOLD signal for the water condition compared to other conditions was: (a) greater in M1 than sour; (b) greater in ACC, IFG opercularis and triangularis and IPG than e-stim; and, (c) greater in S1 than visual. BOLD signal for the sour compared to other conditions was: (a) greater in SMA than water; (b) greater in IFG opercularis than e-stim; and, (c) greater in S1 than visual. The visual condition had greater BOLD response in: (a) ACC than e-stim; and, (b) M1 than sour. E-stim was not greater than any other condition. Images of activation for main effects and condition contrasts are found in Figure 3.

Habituation and sensitization

Habituation, or gradually decreasing BOLD signal, was observed in IPG with water. On the other hand, the insula and Rolandic operculum increased signal over time during the visual condition. Also, S1 and IPG gradually increased signal during sour swallows. The largest cluster was the ACC bilaterally for sensitization in water trials (Figure 3). No habituation or sensitization effects were found with e-stim trials.

Discussion

We have shown that different forms of heightened sensation are associated with BOLD signal with different cortical patterns during normal swallowing. To our knowledge, this is the first investigation of the underlying neural substrates involved in both intention- and stimulus-based input during swallowing, many of which are commonly used to augment swallowing in dysphagic patients and experimentally in healthy adults.

Sour condition

A sour tastant is salient and has likely been previously experienced by many adults. The frontal operculum and anterior insula are the primary gustatory cortices according to clinical studies, but fMRI investigations show a wider distribution of network activation for taste (Cerf-Ducastel et al., 2001; Small, 2006). We also show activity in the right anterior insula and frontal operculum during sour bolus swallowing (Figure 2). Babaei et al (2010) investigated the effects of a lemon flavored liquid gustatory and olfactory stimulation on swallowing BOLD response in healthy adults. They concluded, overall, that flavor increases cortical activation in the swallowing neural network (sensory-motor cortex, insula, cingulate gyrus, prefrontal cortex, precuneus) compared to saliva and water swallows (Babaei et al., 2010). Babaei et al (2010), however, only analyzed and reported findings for the left hemisphere, so direct comparisons cannot be drawn between theirs and the current investigation, since our sour condition had BOLD response also in the right hemisphere (SMA, IFG opercularis, S1).

Visual biofeedback

The use of visual biofeedback increases one's awareness about the state of the body, typically during a physical activity. Swallowing movements are internal and not readily seen, so biofeedback is used clinically to help to augment swallowing kinematics by accessing intention-based or endogenous input. Biofeedback is commonly combined with novel swallowing treatment maneuvers such as effortful swallowing or the Mendelsohn maneuver, which have been associated with wide-spread BOLD activation (Peck et al.). Most reports indicate greater improvement in patients when biofeedback is combined with swallowing or swallowing maneuvers than without (Crary et al., 2004; Felix et al., 2008; Reddy et al., 2000). Others have reported that visual and auditory stimuli consisting of swallowing videos and/or sounds are associated with BOLD response in SMA, premotor and primary motor areas (Kawai et al., 2009). Our visual biofeedback task was characterized by a neural pattern of primarily frontal regions for motor planning. Less activation in S1 than water and sour suggests that the visual stimulus might direct more attention to motor planning for swallowing.

Cutaneous electrical stimulation

E-stim on the skin overlying the anterior neck has been shown to reduce incidences of ingested material entering the airway (a measure of swallowing severity) in patients with chronic pharyngeal dysphagia (Ludlow et al., 2007). Overall, the e-stim condition activated fewer regions within our selected ROI, including primarily insula and M1 during swallowing. This does not mean, however, that other cortical regions are not active at lower thresholds in the e-stim condition. It does suggest, however, that overall, sour, water, and visual swallowing conditions may have more potential for activating S1, IFG tri, IFG oper, ACC, IPG, and SMA compared to e-stim. We are cautious, however, not to imply that activating a more diverse cortical pattern suggests greater therapeutic potential (or the reverse for that matter), as this may not be a valid conclusion.

E-stim is a novel and, sometimes, painful sensation. When applied to the finger it has been associated with BOLD response in the sensorimotor cortex, insula, and DLPFC (Alkire et al., 2004). Galvanic stimulation was applied to the neck bilaterally, activating medial insula and anteromedial thalamus (Bucher et al., 1998). Left insular activity is also associated with electrically induced dental pain (Rudenga et al.). This suggests that activation of the insula is common with electrical stimulation, and possibly associated with its discomfort. Fraser et al applied pharyngeal electrical stimulation at 5 different frequencies (10 minutes each) followed by fMRI and reported significantly greater BOLD signal bilaterally in M1 and S1 during water swallowing compared to water swallowing not preceded by pharyngeal electrical stimulation (sham stim) (Fraser et al., 2002). Future studies are needed to determine the importance of location, time and duration of electrical stimulation on BOLD signal for swallowing.

Habituation and sensitization

To our knowledge, this is the first investigation of habituation or sensitization of BOLD response in normal swallowing. Other studies have investigated these phenomena outside of swallowing. Habituation occurred within sensorimotor and motor planning regions with esophageal stimulation with other sensory modalities (Coen et al., 2007) and within taste-related cortical regions with gustatory stimuli (Wagner et al., 2006). Dessirier et al (2000) reported significantly increased lingual irritation evoked with citric acid (Dessirier et al., 2000) and the somatosensory system is associated with lingual irritation (Kandel, 2000). In our data, the largest cluster (221 edge-connected voxels) was found bilaterally in the ACC for sensitization with water swallowing. The ACC facilitates implementation of a targeted action (Paus et al., 1993) and plays a role in stimulus processing and response generation (Buchel et al., 2002). Water swallowing is often used as a control condition in swallowing studies. Our data suggest that, with repeated exposures, the cortex might gradually modify its processing of water swallows, which is justifiable since swallowing water involves a sensory stimulus followed by a targeted motor response.

Regarding the sensory conditions, more research is needed to understand whether (and to what extent) gradual changes to swallowing kinematics with heightened sensation habituate possibly minimizing therapeutic benefit over time. Theunissen et al (1996, 2000) showed that mouth movements during the tasting process inhibit adaptation to taste stimuli. These authors assert that previous laboratory-based studies may have found taste habituation using filter paper, but that real-life eating situations, do not show a comparable amount of taste intensity loss (Theunissen and Kroeze, 1996; Theunissen et al., 2000). Our study involved swallowing a sour bolus, which requires lingual movement and could explain why we did not see substantial decreases in BOLD signal over time.

Limitations and strengths

The goal of this study was to identify the neural substrates of important sensory modalities already known to modulate swallowing kinematics. Including healthy adults across the age-span makes our findings more generalizable. Behavioral swallowing measures, such as videofluoroscopy, were not within the scope of this investigation. However, numerous studies have investigated the impact of heightened sensory input on swallowing function, including taste, e-stim and visual biofeedback. A recent and thorough review of such studies highlights the progress made over the years in identifying the effects of sensory stimulation on peripheral swallowing function (Steele and Miller, 2010); this review, albeit indirectly, points to the gaps in our understanding of how these stimuli alter cortical processing. We did not compare young and old directly because the two groups had different head motion associated with the tasks, however the findings can be viewed separately by group (Supplemental Table). This study involves different forms of sensory stimulation and water swallowing and, as in many other fMRI studies of swallowing, effects from one condition might carry over to the other. Some neural stimulation studies (transcranial magnetic stimulation or TMS) have reported long-term changes in cortical excitability with taste and electrical stimulation in swallowing musculature. We aimed to minimize these potential carry-over effects by randomizing the order of the conditions across participants. Our statistical threshold of $p \leq 0.01$ for 70+ edge-connected voxels will include 5% false

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positives and clusters smaller than 70 voxels should be interpreted with caution. Finally, this fMRI study required participants to swallow supinely while liquid was infused into the oral cavity with small tubes, making swallowing more challenging than in a normal seated position without tubes in the mouth. Also, swallowing involves head movement, which can cause artifacts in the results. Though we regressed out spin history artifacts due to motion using realignment parameters, motion effects may not have been completely eliminated. Hence, activations detected near tissue boundaries must be interpreted with caution.

Conclusions

We conclude that these sensory modalities have distinct cortical patterns when overlaid with swallowing for both intention- and stimulus-based inputs. Our findings also warrant future studies of whether the insula plays a particular role in initiation with increased sensory input. Taken together, these findings begin to lay the groundwork for a formulaic approach to treating neurogenic dysphagia wherein affected cortical areas that need additional stimulation might be targeted with a fine-tuned sensory treatment. Taste, cutaneous electrical stimulation, and visual biofeedback are already being used clinically, however tailoring these treatments to neural substrates may prove more effective in dysphagia rehabilitation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. Study examines endogenous and exogenous swallowing stimulation with fMRI
2. Study includes adults across the age span
3. Study examines habituation and sensitization during swallowing

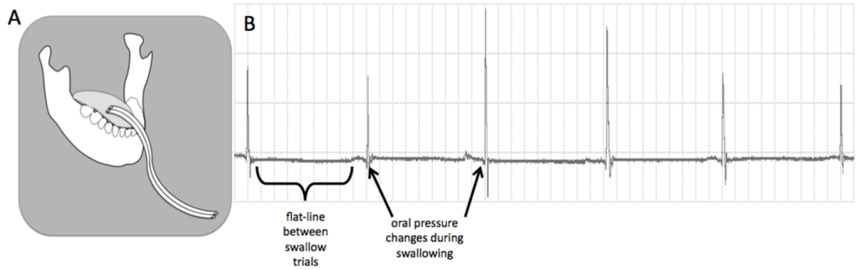

Figure 1.

(A) Approximate location of plastic tubes in the mouth. (B) The oral pressure signal is shown from one participant during the visual biofeedback condition with a flat-line (no swallowing) between each swallow (peaks).

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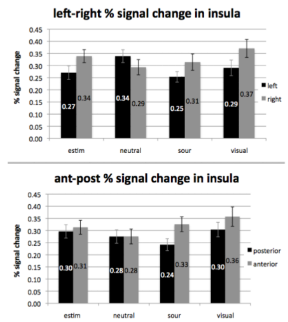

Figure 2.

Mean peak percent BOLD signal change within the insula displaying left-right differences and anterior-posterior differences across conditions in all participants.

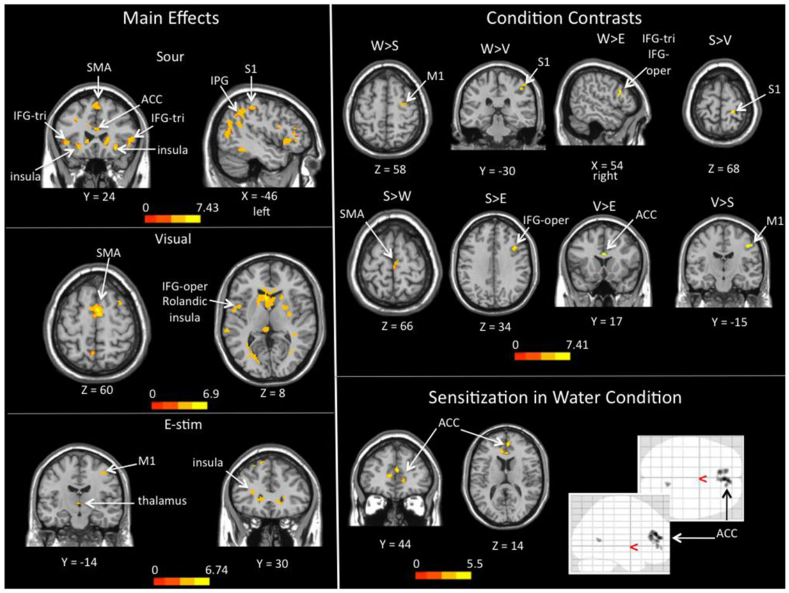

Figure 3.

Images of BOLD response of main effects, condition contrasts, and sensitization (water condition). Left side of brain is left hemisphere for y and z. Abbreviations: ACC-anterior cingulate cortex, IFG oper-inferior frontal gyrus opercularis, IFG tri-inferior frontal gyrus triangularis, IPG-inferior parietal gyrus, M1-precentral gyrus, SMA-supplementary motor area, S1- postcentral gyrus. Glass brains shown for water sensitization.

Table 1

Suprathreshold regions for main effects, condition contrasts, and habituation and sensitization. Y=young; O=old.

		Cortical Region							
	Condition	**M1**	**S1**	**ACC**	**Insula**	**SMA**	**IFG opercularis**	**IFG triangularis**	**IPG**	**Rolandic operculum**
Main Effects	**water**	right	both	both			right		both	
	sour		left	both	both	both	left	both	both	
	estim	right			left					
	visual			both	both	both	both	left	right	left (O)
ConditionContrasts	**water > sour**	right (Y)								
	water > estim			left (Y)			both	both	both	
	water > visual		right							
	sour > water					right (O)				
	sour > estim						right (O)			
	sour > visual		right (O)							
	visual > estim			left (Y)						
	visual > sour	right								
Habituation Sensitization	**water**								left (O)	
	water			both (Y)						
	sour		left						left	
	visual				left					left (Y)