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Swallowing intentional off-state in aging and Alzheimer's disease: preliminary study

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Abstract

Frontal cortical activation is elicited when subjects have been instructed not to initiate a sensorimotor task. The goal of this preliminary fMRI study was to examine BOLD response to a "Do Not Swallow" instruction (an intentional "off-state") in the context of other swallowing tasks in 3 groups of participants (healthy young, healthy old, and early Alzheimer's or AD). Overall, the older group had larger, bilaterally active clusters in the cortex, including the dorsomedial prefrontal cortex during the intentional swallowing off-state – this region is commonly active in response inhibition studies. Disease-related differences were evident where the AD group had significantly greater BOLD response in the insula/operculum than the old. These findings have significant clinical implications for control of swallowing across the age span and in neurodegenerative disease. Greater activation in the insula/operculum for the AD group supports previous studies where this region is associated with initiating swallowing. The AD group may have required more effort to "turn off" swallowing centers to reach the intentional swallowing off-state.

Keywords

Alzheimer's disease; fMRI; deglutition; cognitive aging

INTRODUCTION

Swallowing involves many complex sensorimotor events that are not thoroughly understood. Normal swallowing has both volitional (oral) and non-volitional (pharyngeal) components, which couple seamlessly to move ingested material safely into the esophagus when swallowing. Swallowing is associated with cortical activity when elicited spontaneously

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(response to saliva build up) and in response to a command [1, 2]. However, to broaden the understanding of volitional control of sensorimotor motor tasks, such as swallowing, investigations of intention, internal selection, and inhibition are becoming more frequent in the literature. Others have argued that intentional action may involve decisions of what and when to act and, in more recent studies, *whether* to act [3]. Studies on decisions *whether* to act center on activation of the medial frontal cortex. Neural imaging studies of swallowing indicate multiple cortical regions are involved in healthy younger and older adults [4, 5]. However, cortical changes with neurological damage might cause under-activity in neurodegeneration, such as Alzheimer's Disease (AD) [6], prompting further research of swallowing within healthy aging adults and those with neurological disease.

Most of our current understanding of sensorimotor behavior requires participants to perform the task of interest. However, a growing body of knowledge has enriched our view of motor perception, planning and performance by examining, not only self-executed motor tasks, but also intentional off-states, imagination and observation of an action [7–9]. For example, the left inferior frontal gyrus (IFG) or Broca's area is critical for initiating a speech task, whereas the right IFG is active when healthy adults comply with instructions to avoid producing speech [10]. Findings such as these have helped to establish models of hemispheric dominance for planning speech initiation and inhibition. They also provide a baseline for gauging alterations caused by healthy aging or neurological disease. For swallowing, the go, no-go paradigm was used with functional magnetic resonance imaging (fMRI) in healthy young adults to dissociate BOLD responses to the visual swallowing cues from actual swallowing [11]. This was not a traditional response-inhibition study because the no-go task did not involve a bolus stimulus for the participant to suppress, possibly because it could be unsafe for participants to hold liquid in the posterior oral cavity and inhibit swallowing while lying supinely. Nonetheless, as expected, discrete cortical regions (pre- and post-central gyri, insula, anterior cingulate cortex, frontoparietal opercula) were active during the “go” task (saliva swallow) and not during the “no-go” state (no swallow performed), effectively separating the visual command to swallow from the sensorimotor behavior of swallowing.

Impaired executive functioning is often reported with healthy aging and, to a greater degree, in neurodegenerative diseases such as AD. More specifically, compliance with a “do not” command for motor tasks involves executive control over motor regions for initiation, which also changes with age and in the early phases of AD [12, 13]. Studies of response-inhibition show that AD patients have impairments beyond those observed in healthy aging for both behavior and BOLD response [14, 15].

We have shown that healthy aging and early AD are associated with BOLD differences for execution of various swallowing conditions [6, 16]. Central control of motor-related tasks can inform models for diagnosis and treatment of dysphagia (swallowing impairment). In this preliminary study we examined age- and AD-related differences in BOLD response for an intentional swallowing “off-state” or compliance with performing a “Do Not Swallow” (DNS) command during fMRI. The goal was to understand the intentional swallowing off-state differences among healthy young and old adults and in early AD, as they have known differences in swallowing [6, 16]. We propose that BOLD differences for an intentional swallowing off-state will involve (a) similar cortical regions as in other traditional response inhibition fMRI studies in our healthy groups, although with greater BOLD response in the older group and (b) differences in cortical activation patterns with disease. A secondary goal was to determine whether laterality differences exist in the intentional swallowing off-state across the three groups. We expected that activation in the young group would be more lateralized to the left than in the healthy old or AD group.

MATERIALS AND METHODS

Thirty-six participants completed this study (12 young: average age 27.9, range 23–37, SD 4 yrs; 11 old: average age 72.3, range 64–83, SD 7.5; 13 AD: mean age 74.3, range 58–88yrs, SD 8.6yrs). All healthy participants were without dysphagia and reported no previous speech, language, or chronic medical conditions. All AD participants had mild dementia characteristic of AD, but were without significant medical, neurologic, or psychiatric illness not related to AD after comprehensive clinical evaluation. Mini Mental State Examination scores were obtained for the older participants (healthy old: mean 28, SD 2.3; and AD: mean 23, SD 2.1). No subject was depressed, had a Hachinski Ischemia Scale score greater than 4, or other medical condition besides AD that could account for the dementia. Although the AD group did not exhibit significant aspiration or penetration during swallowing due to dysphagia, they did have significantly shorter durations of laryngeal vestibule closure than the healthy older group at this early stage in the disease [6]. Laryngeal closure during swallowing is an important component of airway protection during swallowing. The Institutional Review Board of the University of Wisconsin approved this study and all participants gave written informed consent.

fMRI Procedures

All participants were familiarized with the experimental procedures before beginning the study. In this pilot study, all healthy subjects were presented with 10 visual instructions that read DNS over the course of 3 runs. These DNS cues were interspersed among swallow tasks including 10 saliva (cued visually), 20 water and 20 sweetened thin liquid barium (Varibar® thin) swallows (both cued only by delivery of the liquid). The AD group spent less time in the scanner to improve compliance and completed only 2 runs (7 DNS; 7 saliva; 13 water; 13 barium). During the inter-stimulus intervals, participants were told to attend to the fixation point and were prepared to swallow if they felt a bolus in their mouths or if they saw the “Swallow Saliva Now” cue. Before the start of the study, all participants were instructed to avoid swallowing or making any oral movements when the DNS visual cue was presented before them and that the investigators would monitor whether they are compliant with this task. The entire DNS condition lasted for an average of 13 seconds. Visual cues were viewed through a mirror mounted on top of the head coil using *Presentation* software (www.neuro-bs.com). Compliance with all tasks was confirmed for each participant with real-time monitoring of a pressure transducer that measured changes in the oral cavity during swallowing. The pressure transducer was connected to a water-filled tube that extended from each participant’s mouth and was time-locked with the transistor-transistor-logic (TTL) pulses from the MRI scanner. Responses from the swallowing trials have been previously published [6, 16]. During the fMRI study and at the end of the fMRI study, many participants reported an urge to swallow during the DNS cue.

Functional Imaging

In this event-related study, MR images were collected on a 3.0 T GE Signa scanner (Waukesha, WI) using an 8-channel head coil. Functional image data were obtained with a T2* gradient-echo, echo planar imaging (EPI) pulse sequence optimized for blood-oxygen level dependent (BOLD) contrast with the following parameters: echo time (TE) = 30ms; repetition time (TR) = 2000ms; flip angle = 75°; acquisition matrix = 64×64; and FOV=240mm. With whole brain coverage, thirty 4.5mm thick inter-leaved axial slices were obtained. Each run collected 148 volumes and the first three volumes were discarded to allow for magnetization stabilization. Higher order shimming was applied to the static magnetic field (B0) prior to EPI acquisition.

Additionally, we acquired whole-brain high-resolution T1-weighted Inversion-Recovery 3D spoiled gradient echo (3D-IRSPGR) (TR = 9.592ms; TE = 3.00ms; inversion time (TI) = 600ms; flip angle = 10°; acquisition matrix = 256×256; FOV = 230mm; slice thickness = 1.5mm scans to confirm the absence of structural abnormalities and exclude regions of atrophy.

fMRI Image Processing

All functional images were processed with Statistical Parametric Mapping (SPM5, Wellcome Department of Imaging Neuroscience, University College London, UK) and Analysis of Functional NeuroImages (AFNI, Medical College of Wisconsin, USA) software packages. Images were slice-time corrected, motion-corrected, normalized to the MNI EPI template using a nonlinear transform, re-sampled to 2mm isotropic voxels, and smoothed with an 8mm FWHM Gaussian kernel. All individuals had less than 3mm of movement in the x, y, and z directions and less than 3 degrees of deflection in pitch, roll, and yaw.

fMRI Statistics

For individual participants, a general linear model of the time series data was performed for first-level analyses. Five possible states were modeled: 1) barium swallow, 2) water swallow, 3) saliva swallow, 4) periods with the DNS instruction, and 5) spontaneous swallows at any other point in time. In modeling all of these states, we are comparing DNS condition to all other times when the subject did not swallow. Swallow onset times for barium, water, and saliva conditions obtained from the pressure transducer and visual cue onset times for the DNS condition were all convolved with the canonical hemodynamic response function (HRF) to construct the statistical model. The general linear-model removed the low frequencies with a 128 s high-pass filter. Additionally, vectors were added to the design matrix for the motion parameters and their backward derivatives. Swallows observed with the pressure transducer during the DNS condition were not considered further. Contrasts for DNS from the first level analyses were entered into one-sample t-tests for each group.

Second-level analyses for between group comparisons (young versus old; old versus AD) used T-tests to identify significant group differences. For young and old comparisons and conjunction analyses (overlap) all 10 DNS tasks were compared among 3 runs; for old versus AD comparisons and overlap, only DNS tasks from the first 2 runs (7 total) were compared. Our analyses were further restricted to the cortical regions that are reported in the literature to be involved in swallowing [1, 17] and areas thought to be involved in AD -- the hippocampus, parahippocampus, amygdala, and orbital frontal gyri. All analyses were at the $\alpha=0.005$ uncorrected level and in at least 153 edge-connected voxels corresponding to a cluster level $\alpha=0.05$.

We excluded areas of significant difference in gray matter volume as determined by a two-sample t-test ($p<0.001$ in at least 50 contiguous voxels) controlling for total brain volume using posterior probability derived from VBM5 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) in SPM5. This exclusion is necessary to ensure that significant differences are based on comparisons of functional activity rather than artifact due to disease-related atrophy (AD) or age-related atrophy (healthy old).

Laterality—Regions that were activated from the voxel-wise analyses in this study were used to select a priori ROI from the Automated Anatomical Labeling Atlas [18] for an exploratory post-hoc comparison of laterality. These regions are the same as the swallowing and cognitive masks described above. BOLD signal was extracted from each region in each subject and the following equation (L-R) was used to determine a laterality score. These

scores were then entered into within group and between group non-parametric tests (pair-wise Wilcoxon) to establish whether there was laterality and whether it differed by group. Because laterality in this study is an exploratory analysis to obtain hypothesis-generating information about laterality for this task, we used a liberal alpha value for significance (one-sided $p \leq 0.05$).

RESULTS

All participants were able to complete the study. Based on data from our oral pressure transducer, healthy young adults were compliant 94% of the time (no swallow signal during the DNS condition) and the healthy older adults and AD groups were somewhat less compliant (83% old; 87% AD).

Group Contrasts for DNS

We compared (a) healthy young to old to determine age-related differences in the task and (b) old to AD to determine disease-related differences in the task (Table 1). No significant regions were active for young>old or old>AD contrasts. The older adults had greater clusters of activation than the young bilaterally in the middle and superior frontal gyri, in the left parahippocampus, middle temporal pole and inferior orbital frontal gyrus, and in the right middle temporal gyrus and inferior frontal triangularis (Figure 1). Only the left anterior insula was more active for the AD than the old (Figure 2).

Within Groups Results for DNS

Young and Old overlap—Positive clusters included multiple cortical regions bilaterally within the frontal, temporal and parietal lobes as well as the insula, middle and posterior cingulate, amygdala, hippocampus and parahippocampus (Supplemental Table 1; Figure 1). The right mid temporal pole was unique to the young group and the right frontal superior medial gyrus was unique to the old group. Responses within only the young group included both positive and negative activity; deactivation in the young was found in the bilateral anterior cingulate gyri and right frontal superior medial gyrus (Supplemental Table 2).

AD and Old Overlap—Positive clusters include many of the same cortical regions as in young and old overlap above, excluding the left amygdala, right middle cingulate, and left superior temporal gyrus, which were not active in the AD group at our set threshold (Supplemental Table 1; Figure 2). Also, uniquely active in the AD group, relative to the healthy old, are the right superior orbital frontal gyrus and left superior frontal medial gyrus (Supplemental Table 2).

Laterality

Multiple cortical regions were significantly lateralized for the DNS task. Only the middle frontal gyrus and precuneus were lateralized in all three groups and lateralized to the right hemisphere (Figure 3). Between-group comparisons indicated that with age and disease, laterality shifted away from the left hemisphere for the DNS task.

DISCUSSION

Findings of this preliminary investigation indicate that the intentional swallowing off-state, in the context of other swallowing tasks, is associated with BOLD responses within multiple cortical regions in healthy and cognitively impaired individuals. In fact, group contrasts show that the cortical regions associated with the greatest BOLD responses for this task differ primarily by disease state, but not by age. Overall, active regions include some traditional swallowing areas as well as those involved in attention and decision-making.

Healthy adults

Healthy older adults showed more BOLD response primarily in frontal and temporal regions. Specifically, suprathreshold clusters of frontal activation in Brodmann's area 9 or BA9, BA10, BA45, and BA46 overlap with previously published studies of inhibition [9, 19–23]. Our participants were unaware of whether the upcoming task would be a swallow stimulus (bolus infused into oral cavity), a command to swallow their saliva, or a command not to swallow. Thus, activation of inhibitory areas during the DNS task suggests that healthy young and old adults were prepared to swallow until they saw the DNS command. Furthermore, our old > young comparison supports previous studies of response inhibition showing increased activation in these frontal areas with advancing age [20, 21, 24]. Increased BOLD response with advanced age was also found in our participants during swallowing [16].

Early Alzheimer's disease

The left anterior insula was the only region with greater activation in AD than old. This area is active in the stages immediately prior to swallowing for planning and initiation [25, 26], when liquid was infused to the oral cavity. Compared to the healthy group, the AD group might have had stronger activation in this swallowing planning area after viewing the DNS command because they required more time to stop planning for a swallow.

However, our old > AD contrast of the “Swallow Saliva Now” command in the same group of participants also showed greater activation within left anterior insula (cluster 59, MNI -36,26,6) [16] as did the AD > old contrast for the DNS command (cluster 326, MNI -35,16,15). This could further substantiate the theory that the left anterior insula is involved in initiating swallows (successful saliva swallows in both groups showed greater insular activation in the healthy group), but that “turning off” planning in this area required more effort in the AD group. Direct studies of intracortical inhibition using transcranial magnetic stimulation (i.e. short-latency afferent inhibition or SAI) and other behavioral studies indicate that (early) Alzheimer's disease involves inhibitory dysfunction in experimental tasks [12, 27, 28]. Furthermore, the insula is one of a few cortical regions that atrophies earlier in the course of the disease [29–31]. In general, some differences in inhibition with AD might be explained by new theories that the anterior insular cortex (particularly the left) is “the hidden side of intentional action” and should be considered alongside the medial frontal cortex for voluntary control of behavior, including forming and evaluating action intentions [32].

Laterality

Our laterality comparisons were exploratory and have revealed some interesting hypotheses for future studies. For the DNS task, there appears to be a difference in lateralization for the young (left) versus the two older groups (healthy and AD, right). Many previous fMRI studies of swallowing report left lateralization in healthy young adults, while our work shows a possible shift to the right hemisphere with age [16, 33]. This suggests that compliance with the intentional swallowing off-state might involve the same age-related shift to the right associated with swallowing.

Strengths and Limitations

This is a pilot study with a small sample size and small number of DNS trials. However, a stringent significance threshold was used to compensate. Participants were not given a stimulus to suppress (liquid infused into the oral cavity) due to the risk of aspiration in the older adults and in the AD groups of our study. We acknowledge that we have little control over the DNS condition and that some participants indeed may be actively inhibiting a

swallow and others may not – others might have been paying added attention to the anatomical region that they were instructed not to move. Still, our findings overlap with response inhibition studies and suggest that context matters, in that participants were at least expecting an infused bolus or a command to swallow at any time. Finally, activity in the insula/opercular region might be due to residual taste or mouth-feel of the sweetened liquid barium in preceding swallowing trials. Nonetheless, this region was only most active in the AD group, not in the healthy groups whose trials followed the same order. Also we found no differences in the sweetened barium swallowing trials between old and AD participants.

This study investigates a sensorimotor behavior that is critical for survival and frequently deteriorates in neurogenic diseases and disorders. The novel findings reported herein provide insight into differential swallowing motor control between healthy aging and older adults with cognitive disease. Implications from these findings could inform other models of stereotypical sensorimotor activity (i.e. locomotion) as well as the process of healthy aging separate from age-related disease. In the future, we aim to conduct a larger scale study with better control of the DNS condition with creative methods for a swallowing stimulus to suppress without compromising participant safety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. BOLD response for intentional swallow off-state for old and young overlapping regions (A – axial; B – coronal) and BOLD response for old > young contrast. Left side of image is left hemisphere for all images.

Figure 2. BOLD response for intentional swallow off-state for old and AD overlapping regions (A – axial; B – coronal) and BOLD response for AD > old contrast. Left side of image is left hemisphere for all images.

Figure 3. Within group means of BOLD signal are plotted for middle frontal gyrus to show this cortical region is lateralized to the right for the DNS tasks in all groups. These data are based on the first 2 fMRI runs for all groups.

Cortical regions with suprathreshold clusters showing BOLD response between groups (old > young and old > AD)

Table 1

Between Groups Contrasts						
cluster	T	Old > Young			z	location
		x	y			
172	6.15	-55	18	-32		L. Mid Temporal Pole
458	4.37	-23	35	35		L. Mid Frontal
	4.25	-44	30	48		L. Mid Frontal
	3.21	-18	36	64		L. Sup Frontal
223	4.1	-10	-2	-20		L. ParaHippocampal
	3.84	-12	10	-26		L. Inf Orb Frontal
207	4.1	32	32	54		R. Sup Frontal
	3.5	47	26	52		R. Mid Frontal
	3.28	42	36	48		R. Mid Frontal
249	3.93	46	-66	17		R. Mid Temporal
194	3.71	42	36	22		R. Inf Frontal Tri
AD > Old						
cluster	T	x	y	z		location
326	4.35	-36	18	14		L. Anterior Insula