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Normal Swallowing and Functional Magnetic Resonance Imaging: A Systematic Review

Ianessa A. Humbert, PhD and **JoAnne Robbins, PhD**
William S. Middleton Memorial Veterans Hospital, Department of Medicine, University of Wisconsin-Madison, Madison, Wisconsin, USA

Abstract

Unknowns about the neurophysiology of normal and disordered swallowing have stimulated exciting and important research questions. Previously, these questions were answered using clinical and animal studies. However, recent technologic advances have moved brain-imaging techniques such as functional magnetic resonance imaging (fMRI) to the forefront of swallowing neurophysiology research. This systematic review has summarized the methods and results of studies of swallowing neurophysiology of healthy adults using fMRI. A comprehensive electronic and hand search for original research was conducted, including few search limitations to yield the maximum possible number of relevant studies. The participants, study design, tasks, and brain image acquisition were reviewed and the results indicate that the primary motor and sensory areas were most consistently active in the healthy adult participants across the relevant studies. Other prevalent areas of activation included the anterior cingulate cortex and insular cortex. Review limitations and suggested future directions are also discussed.

Keywords

Deglutition; Deglutition disorders; Functional magnetic resonance imaging

An estimated 18 million adults have dysphagia, or swallowing disorders, in the United States [1]. Dysphagia is a condition that becomes more prevalent with increasing age and often results from neurologic damage or disorders such as stroke, Alzheimer's disease, and Parkinson's disease. As a result, much of the research on swallowing disorders has focused on understanding and delineating the neurophysiology of swallowing with the overall goal of increasing the efficacy and accuracy with which diagnosis and intervention procedures are employed.

Data from clinical and animal studies have provided the earliest insight into the central control of swallowing. In particular, clinical studies have provided an evolving foundation of thought pertaining to the central control of swallowing. These investigations have characteristically started with a disordered neurologic group (i.e., poststroke population) and combined both anatomical brain-imaging techniques (still pictures of the brain) such as computerized tomography (CT) and/or magnetic resonance imaging (MRI) with a swallowing assessment to correlate damaged brain areas with the presence or type of dysphagia observed. The vast majority of clinical studies have focused on the effects of stroke on swallowing [2-15]. Far fewer clinical studies have focused on swallowing in other neurologic conditions such as Parkinson's disease [16-20], Alzheimer's disease [21-25], or traumatic brain injury [26-30].

Correspondence to: Ianessa A. Humbert, PhD; Department of Medicine, University of Wisconsin-Madison, 2500 Overlook Terrace (11G), Madison, WI, 53705, USA; E-mail: humbert@wisc.edu.

Clinical studies are limited in that they add incomplete insight into the central control of normal swallowing. In other words, clinical studies that include subjects with neurologic disorders and dysphagia result in inferred ideas about how normal swallowing is controlled. A full understanding of normal swallowing neurophysiology is important for contrasting disordered neurophysiology.

Recent advances in medical technology have facilitated functional brain-imaging studies of swallowing and swallowing-related activities (i.e., lingual movement). Numerous techniques have been applied to investigate functional brain activity during swallowing (primarily in healthy individuals), including positron emission tomography (PET) [31-34], magnetoencephalography (MEG) [35-39], transcranial magnetic stimulation (TMS) [31, 40-42], and electroencephalography [43-45] (EEG). Functional MRI (fMRI) has been especially useful in studying brain activity during swallowing in normal individuals, mainly because of its high spatial and temporal resolution (ability to detect changes in an image across different spatial locations and over time) for various tissue types, its lack of use of radiation or need for other invasive procedures (needle injections), and its ability to obtain images in any plane [46]. In addition, fMRI has become increasingly available for research purposes and has seen tremendous technologic development since its inception, with promise for continued advancement.

This systematic review summarizes studies that have explored the neurophysiology of swallowing in healthy adults using fMRI. The goal of a systematic review is to gather and present objectively the current status of research in a particular area of interest. It presents an unbiased review of the relevant literature by describing the systematic methods for obtaining the relevant literature on this topic.

Search Strategies

Electronic

An electronic database search was completed using Medline (Ovid and PubMed), CINAHL, DARE, ACP Journal Club, the Cochrane Library, AgeInfo, Best Evidence, Health & Wellness, and the World Wide Web (Google Scholar).

Hand Searches

Ancestral searching was used to search the reference lists of papers that were retrieved electronically. Mesh headings used in Medline electronic databases included “deglutition AND functional magnetic resonance imaging OR functional MRI OR fMRI,” “deglutition AND brain OR brain mapping,” and “deglutition AND diagnostic imaging.” For electronic databases that do not prefer or require Mesh terms (i.e., Google Scholar), the following terms were used: “deglutition,” “swallow,” “swallowing,” “brain,” “fMRI,” “functional magnetic resonance imaging,” “functional MRI,” and “diagnostic imaging.”

Search Limitations

This systematic review has a fairly narrow scope and, as a result, likely yielded fewer peer-reviewed journal articles than broader subject areas. Therefore, fewer search limits were used in an attempt to attain a larger number of papers for perusal. Whenever possible, electronic searches were limited to studies of adults, humans, and the English language.

Inclusion Criteria and Data Extraction

The titles and abstracts of studies found with each search were reviewed to determine which studies warranted further review of the full-text version. Full-text studies were considered relevant if they included (1) adults who swallow normally, (2) fMRI as the brain-imaging technique, (3) a swallowing task while the subject was in the scanner. Only research studies were included; all review papers were excluded.

The following information was extracted from the relevant full-text studies:

1. Number of study participants
2. Age (average and range) of study participants
3. Study design (block, event-related, both)
4. Brain location focus (i.e., cortical, subcortical)
5. Tasks (i.e., saliva swallow, water swallow, finger tapping)
6. Swallowing stimuli (i.e., visual, auditory, infused bolus)
7. Planes of image acquisition (axial, coronal, sagittal)
8. Swallow monitoring technique (i.e., surface electromyography)
9. Results/conclusions (locations of activity)

Description of the Review

A total of 70 articles were retrieved. Of these, 20 used fMRI and were chosen for full-text review. Six additional articles were excluded for reasons that include:

1. No swallowing task during fMRI scanning procedures [47-50]
2. Blood oxygen level-dependent (BOLD) signal changes not reported [51]
3. Healthy volunteer data are from previous research that is already included in this review [52]

Results

Fourteen articles that used fMRI in healthy adults while swallowing were relevant and are detailed in Table 1 [41,53-65].

Subject Number and Ages

The number of subjects in the relevant studies ranged from 6 to 14 (mean = 9.2). One study [56] reported including 14 subjects; however, it included only the 10 subjects who reportedly participated in the two sub-studies with swallowing tasks in that particular study. Another study [53] did not report the number or ages of subjects in the study. Two studies [53,61] did not report the ages of the subjects in the study, but all other studies reported either the average age, the age range, or both. Considering all of the studies that provided average-age data, the average age of the study participants was 35.6 years and the overall age range of the subjects in the relevant studies was 21–82 years.

Design

The fMRI design of each study was either block, event-related, or both. In a block design, trials from each condition are grouped in time and a rest period is often incorporated (control or null-task blocks) so that activity related to particular tasks can be measured [46]. Six studies used only block designs [41,58,61-64] that incorporated activity (i.e., swallow, nonswallowing motor task) and rest intervals.

The event-related (or single trial) design assumes that neural activity related to a particular task has a discrete interval that can be best captured when not restricted to predetermined or specified time blocks [46]. Six studies in this review used only event-related designs [54,55, 57,59,60,65]. Two additional studies used both block and event-related designs to compare and contrast the two data acquisition methods during swallowing [53,56].

Tasks

The tasks in the relevant studies included swallowing different bolus types (i.e., water, saliva) under different circumstances (i.e., volitional command or “automatic” bolus infusion). Other motor tasks included swallow-related tasks (i.e., tongue-tapping or elevation, lip-puckering or pursing) and non-swallow-related tasks (i.e., finger-tapping). Finally, non-motor tasks often included intentional rest or “no-swallowing” periods.

In fMRI experimental design, the experimental task(s) (i.e., swallowing) is often compared with a control task (i.e., baseline condition or non-task condition) [46]. Among the relevant studies chosen for this review, four studies made comparisons only between swallowing (experimental task) and a rest or no-swallowing task [55,58,64,65]. These studies were either single-task studies or studies with multiple tasks that were all compared with rest, and the rest condition was not always explicitly indicated [55,58]. However, the rest condition is often implied in fMRI studies. On the other hand, other studies clearly indicated that an “off” swallow [64] or “no-go” [65] task was included. Swallowing was also compared with motor tasks that were non-swallow-related [53,62,63], swallow-related [56], or both [60]. Swallows of different types were compared with each other (i.e., saliva and water swallows) [41,54,57,59], and comparisons were made between different types of swallows and non-swallow-related tasks [61].

Brain Location and Plane(s) of Image Acquisition

Each relevant study indicated the location of interest within the brain. These areas of focus include cortical [41,53,54,56,61,63], cortical and subcortical [55,57,59,60,62,65], lower brain stem and cervical spinal cord regions [58], and the cerebellum and basal ganglia [64].

Stimulus Type and Swallow Monitoring

Swallowing was stimulated primarily by visual, auditory, and tactile means. Visual cues were provided using written instructions, drawings, or even flashlight [41,53,54,60,65] and auditory cues were typically instructions given by the investigator [64]. Some studies used subject self-infusion of a water bolus as a swallow stimulus [55] or varied the stimulus depending on the task [57,58,61-63] (i.e., saliva swallow used an audio cue and water swallow was initiated by water infusion).

Nine studies used some technique to confirm that swallowing took place or was absent. These techniques primarily included surface electromyography (EMG) under the chin and/or on the neck to detect movement of the muscles of the larynx [57,61-63] or MR-compatible bellows to measure movement of the larynx and the thoracic cavity (respiration) [54,59,60,65].

Location of Voxel Activation

Each relevant study used BOLD signal change as its primary dependent variable. Most studies expressed this change as “activation” or “voxel activation” in particular locations of the brain as the endpoint. This review summarizes the predominant or consistent locations of activation related only to swallowing tasks across subjects from the 14 relevant studies.

The primary motor cortex (M1, precentral gyrus, Brodmann’s area 4) was found to be active in all but one study and, therefore, was the most prevalent region of activation. The second most prevalent region was the primary sensory cortex (S1, postcentral gyrus, somatosensory cortex, Brodmann’s area 3, 2, 1). Activation was common in the insula and the anterior cingulate gyrus, but only a few studies found activation in the prefrontal, parietal, or temporal lobes consistently or across subjects. Finally, there was little agreement regarding activation in the supplementary motor area, premotor area, internal capsule, thalamus, basal ganglia, cerebellum, putamen, globus palidus, or supramarginal gyrus.

Discussion

Functional MRI is among the fastest-growing brain-imaging technologies. It is advantageous because it is minimally invasive compared with some other brain-imaging systems and is becoming increasingly accessible for research purposes. The disadvantages are that it is an expensive tool to use, is highly susceptible to motion artifact, and commonly requires individuals to lie in the supine position during scanning, which is not a familiar position for swallowing more than one's ambient saliva.

Each of the relevant studies that were included in this review used functional MRI to study normal swallowing in adults. The average number of study participants was nine. Functional MRI lends itself to considerable intrasubject and intersubject variability. Intrasubject variability can result from inconsistencies in the pattern of brain activity during a task in a single subject, while intersubject variability can include both intrasubject variability and differences across subjects for a given task [46]. Intra- and intersubject variabilities can affect the investigator's ability to make reliable inferences from their fMRI data. It has been recommended that power analyses for fMRI studies be based on calculations of the underlying neural activity from a study with a similar paradigm [66].

Dysphagia is more prevalent in older adults within the United States, partly because of higher incidences of neurologic disorders or damage with increasing age. Physiological changes in oropharyngeal swallowing begin to manifest in individuals over 60 years of age [67,68]. The relevant studies in this review that provided age data had an average age of 35 years. Only one study focused on the swallowing neurophysiology of older adults [54]. These pioneering studies of normal swallowing using fMRI included primarily younger individuals, probably because of increased procedure tolerance and homogeneity, reducing intersubject variability that can arise by including both young and elderly individuals. However, individuals with neurologic causes of dysphagia are in great need of research that aims to understand and ameliorate the underlying neurologic constructs that result in dysphagia. Therefore, more future fMRI studies should focus on normal aging and swallowing to enhance what is known about the nature of normal swallowing neurophysiology in older individuals.

The more recently published studies used in this review answered increasingly complex questions with less simplistic task comparisons than earlier studies. For example, an earlier single-task study (1999) used lower-level comparisons of swallowing and an implied rest condition [55], while a later study (2005) compared swallowing to an intentional, visually cued "No Swallow" condition and, thereby, deduced the effects of visual cues on the swallowing signal, making the act of swallowing the primary difference between tasks and enhancing regions of interest related to swallowing [65]. In addition to more complex tasks and research questions, future studies should consistently monitor swallowing presence and absence during fMRI scanning. While the most sensitive techniques for visualizing swallowing (i.e., videofluoroscopy) cannot be used concurrently with fMRI because of limitations of current technology, other means have been used to strengthen study results (i.e., EMG). Swallowing can be highly automatic and difficult to inhibit if saliva has accumulated in the back of the throat while lying in the supine position. As a result, subjects may swallow unintentionally during rest or "don't swallow" conditions, which are often used as control tasks in fMRI studies. Swallow monitoring allows the investigator to discard data in which the participant did not comply with the instructions.

The summarized results from this review indicate that the primary motor and sensory areas are consistently active across healthy adult subjects when swallowing during fMRI scanning. The anterior cingulate cortex and insular cortex were also prevalent in activation during swallowing. Future studies are needed to understand more complex neurophysiologic controls for normal swallowing in areas other than the cortex and subcortex. These might include common pathways and functional modules, white matter tracts, and cerebellum, brain stem, and peripheral neurologic systems. To enlighten understanding of these anatomical landmarks and systems for swallowing, researchers will need to venture into novel tasks and research paradigms and widen research partnerships by including individuals and theories that have derived from disciplines other than their own. Finally, while fMRI is a valuable method for learning about swallowing control, research should also consider other brain-imaging technology to learn more about the neurophysiology of swallowing.

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Table 1

Author, Date	N	Age (range and/or avg.)	Design (fMRI)	Brain Location Focus	Task(s)	Stimuli	Plane of Image Acqui-sition	Swallowing monitoring	Results: Location of voxel activation (Swallowing Tasks only, group data)
Birn, 1999	6	not reported	block and event-related	Cortical	(1)speaking out loud (2) swallowing (saliva) (3)jaw clenching (4)tongue movement (5)finger-tapping	visual (cued by flash light)	axial	none reported	motor cortex
Hamdy, 1999	10	32 avg. 22–61 yrs	event-related	cortical, subcortical	20 wet swallows (water-infused bolus)	water infusion	axial	pneumographic belt	anterorostral cingulate cortex, caudolateral sensorimotor cortex, anterior insula, frontal opercular cortex, superior premotor cortex, anteriomedial temporal cortex, and precuneus.
Mosier, 1999a	8	34 avg.	block	Cortical	(1) 10 sec saliva swallow (2) 10 sec wet swallow (3) 15 sec saliva swallow, (4) finger tap	“instructed” and self-infusion of water	axial and coronal	EMG	**10- and 15-second tasks:** bilateral primary motor cortex (mid precentral gyrus) in all subjects. Activity also identified in primary somatosensory cortex, supplementary motor cortex, prefrontal cortex, transverse temporal gyrus, insular cortex, internal capsule
Mosier, 1999b	8	39 avg.	block	cortical, subcortical	(1) 10 sec saliva swallow (2) 10 sec water swallow (3) 15 sec saliva swallow, (4) finger tap	audio and self-infusion of water	axial and coronal	EMG	**10- and 15-second tasks:** primary motor cortex bilaterally in all subjects. Activation also in primary somatosensory cortex, supplementary motor area, prefrontal cortex, superior temporal

Author, Date	N	Age (range and/or avg.)	Design (fMRI)	Brain Location Focus	Task(s)	Stimuli	Plane of Image Acqui-sition	Swallowing monitoring	Results: Location of voxel activation (Swallowing Tasks only, group data)
									gyrus, insular cortex, transverse temporal gyrus, cingulate gyrus, association areas, sensori-motor integration areas, thalamus, and internal capsule
Kern, 2001a	8	24–27 yrs	event-related	cortical, subcortical	(1) volitional swallow (2) relfexive swallow	tap on the leg (vol. swallow) and infusion of water (reflx. swallow)	sagittal	EMG	**Reflexive:** bilateral activity in primary sensory and motor regions **Volitional:** bilateral activity in primary sensory and motor regions as well as insula, prefrontal, anterior cingulate, and parieto occipital regions
Kern, 2001b	10	21–42 yrs	block and event-related	Cortical	(1) lip pursing (2) tongue rolling (3) jaw clenching (4) volitional swallow (saliva)	tap on the leg	axial and sagital	none reported	anterior cingulate, motor/premotor cortex, insula, occipital/parietal region
Martin, 2001	14	28 avg. 22–34 yrs	event-related	cortical, subcortical	(1)naïve swallow (sbj unaware that swallowing being tested) (2) voluntary (saliva) (3) swallow (water)	"instructed" (voluntary saliva and water)	axial, coronal and sagittal	MR-compatible bellows (larynx)	**Naïve, voluntary and water:** lateral precentral gyrus, lateral post-central gyrus, right insula. Caudal anterior cingulate cortex activated with voluntary and water swallows sigificantly more than naïve swallows.
Mosier, 2001	8	not provided	block	cortical networks	(1) 10 sec saliva swallow (2) 10 sec wet swallow (3) 15 sec saliva swallow, (4) finger tap	audio and self-infusion of water	axial and coronal	EMG	Activation in the sensorimotor cortices, cingulate, premotor cortex, parietal cortex, temporal cortex, basal ganglia and thalamus, insula, and cerebellum. Activation in these

Author, Date	N	Age (range and/or avg.)	Design (fMRI)	Brain Location Focus	Task(s)	Stimuli	Plane of Image Acqui-sition	Swallowing monitoring	Results: Location of voxel activation (Swallowing Tasks only, group data)
									areas were not statistically different among tasks.
Fraser, 2002	8	26 avg. 23–34 yrs	block	Cortical	(1) swallow (water bolus) “on-period” (2) no swallowing “off period” (both tasks occurred after pharyngeal stimulation and sham)	visual	axial	none reported	Sensory and motor cortices had significantly increased voxel activation with pharyngeal stimulation compared to no-stimulation ($p = 0.047$)
Komisaruk, 2002	7	22–57 yrs	block	lower brainstem and cervical spinal cord regions	(1) tongue tapping (2) smile-pucker (3) gaze shifting (4) face brushing (5) finger tapping (6) swallow (saliva and Mendelsohn maneuver) (7) taste	“instructed”	coronal and sagittal	none reported	The nucleus ambiguus was activated 78% of the time during Mendelsohn maneuver (swallow with prolonged laryngeal elevation) and the inferolateral aspect of the motor cortex, just superior to the lateral sulcus (homuncular pharyngeal region) was also active.
Suzuki, 2003	11	24–42 yrs	block	Cerebellum and basal ganglia	(1) swallow (saliva) (2) no swallow	auditory	axial, coronal and sagittal	none reported	Precentral and postcentral gyri, insular gyrus, cerebellum, putamen, globus pallidus across subjects. All bilat except for cerebellum.
Martin, 2004	14	28 avg. 22–35 yrs	event-related	cortical, subcortical	(1) voluntary swallow (saliva) (2) voluntary tongue elevation (3) voluntary finger opposition.	visual	axial, coronal and sagittal	MR-compatible bellows (larynx and tongue)	Largest voxel activation: lat postcentral gyrus, parietal opeculum, supramarginal gyrus (left hem only). Secondary prominent areas: anterior cingulated cortex and

Author, Date	N	Age (range and/or avg.)	Design (fMRI)	Brain Location Focus	Task(s)	Stimuli	Plane of Image Acqui-sition	Swallowing monitoring	Results: Location of voxel activation (Swallowing Tasks only, group data)
									supplementary motor area.
Toogood, 2005	8	23.8 avg. 22–26 yrs	event-related	cortical, subcortical	(1) swallow (saliva, “Go”/“do swallow” condition) (2) relax, don’t swallow (during “No Go”/“don’t swallow” condition)	visual	sagittal	MR-compatible bellows (larynx and resp)	Significantly more activated voxels for “Do swallow” in precentral gyrus ($p = 0.01$), postcentral gyrus ($p = 0.02$), anterior cingulated cortex corresponding to BA24 ($p = 0.04$) and corresponding to BA32 ($p = 0.03$). More active voxels in insula/operculum in “Do” condition, but not significant.
Martin, 2006	9	74.2 avg. 66–82 yrs	event-related	cortical	(1) saliva swallow (2) water swallow (3ml)	visual	axial	MR-compatible bellows (larynx)	**Saliva Swallow:** strong activation in the left pericentral cortex (including perisylvian, primary motor and sensory cortices). Some right pre- and post-central activity. Also prominent were right supplementary motor area, anterior cingulate cortex, superior and middle frontal gyri, inferior parietal lobule, and left insula/ operculum. Less activity in left putamen and thalamus, precuneus/cuneus, lingual gyrus, and fusiform gyrus. **Water Swallow:** largest activation in blateral superior and middle frontal gyri, followed by pericentral cortex. Also prominent were left supplementary motor area, anterior

Author, Date	N	Age (range and/or avg.)	Design (fMRI)	Brain Location Focus	Task(s)	Stimuli	Plane of Image Acqui-sition	Swallowing monitoring	Results: Location of voxel activation (Swallowing Tasks only, group data)
									cingulate cortex, and inferior parietal lobule. Activation also observed in thalamus, precuneus/cuneus, right middle occipital gyrus, and lingual gyrus