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Meta-Analytic Connectivity Modelling of Healthy Swallowing

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Abstract

A quantitative, voxel-wise meta-analysis was performed to investigate the brain regions involved in healthy human swallowing. Studies included in the meta-analysis (1) examined water swallowing, saliva swallowing, or both, (2) included healthy, normal subjects, and (3) reported stereotaxic brain activation coordinates in standard space. Following these criteria, a systematic literature review identified 8 studies that met the criteria. An activation likelihood estimation (ALE) meta-analysis and meta-analytic connectivity modelling (MACM) analysis were performed with BrainMap software. Ten clusters with high activation likelihood were found in the bilateral precentral gyri, right insula, left declive, right medial frontal gyrus, right dorsal nucleus of the thalamus, and the bilateral dentate nuclei of the cerebellum. Meta-analytic connectivity modelling revealed functional two-way and one-way connections between the regions, forming an interconnected network. Together, these finding indicate an extensive swallowing network made up of the key activated regions and the associated areas within those regions.

Introduction

Swallowing is a complex bodily function which transports food or liquid from the oral region to the stomach and is controlled by cortical, subcortical, and brainstem mechanisms. Coordination among several of these brain areas are required to control function in the oral, pharyngeal, and esophageal phases of swallowing. Sensory input involved in swallowing is directed through the trigeminal sensory nuclei and the nucleus tractus solitarius (NTS) (Miller, 2008). The oral phase of swallowing involves the tongue producing a wave-like motion along the central groove to propel any bolus present to the pharynx. In the pharyngeal phase, the jaw-closing muscles stabilize the mandible in a closed position so the suprahyoid muscles can pull the hyoid bone forward and rostrally. The posterior tongue pushes downward and backward into the pharynx as the pharyngeal wall moves forward to meet the tongue. Then a descending wave of contraction moves the bolus down the pharynx. Next the submental muscles raise the hyoid bone before the infrahyoid and pharyngeal muscles raise the larynx. The larynx moves upward and forward toward the hyoid, assisting in the opening of the upper esophageal sphincter (UES) via relaxation in the esophageal phase (Miller, 2008). It is important to understand the neural control of swallowing because while most of the current concepts on motor control and plasticity come from limb movements with contralateral innervation, brain imaging suggests the swallowing muscles are represented in both hemispheres (Sörös et al. 2009). Clinically, knowledge is limited about the neuropathophysiology of impairment, the neuroplastic mechanisms of recovery, or the principles of swallowing rehabilitation. Yet injury to the central nervous system often results in significant swallowing impairment which may require tube feeding.

Early investigations into the networks responsible for swallowing indicated the importance of the pons and medulla in the brainstem (Miller, 2008). The trigeminal (V), facial (VII), glossopharyngeal (IX), vagus (X) and hypoglossal (XII) cranial nerves have all been found to be involved in swallowing. According to a previous meta-analysis on the neural network of swallowing, the lateral precentral gyrus, lateral postcentral gyrus, right insula, cingulate gyrus, paracentral lobule, medial and middle frontal gyrus, putamen, cuneus, and culmen, as well as the inferior parietal lobule and inferior frontal gyrus, were found to be involved in water swallowing (Söros et al., 2009). Additionally, the medial frontal gyrus, cingulate gyrus, postcentral gyrus, precentral gyrus, inferior frontal gyrus, putamen, thalamus, and insula were found to be involved in volitional saliva swallowing (Söros et al. 2009). It is also thought that the sensorimotor cortex may be involved in volitional swallowing (Miller, 2008). However, while some of these foci have been consistently identified in several studies, discrepancies exist such as some studies report bilateral activation of the sensorimotor cortex while others report lateralization, or the exact part of the insula activated varies.

It is possible that these discrepancies result from the use of different methods to identify neural activations during swallowing. Functional magnetic resonance imaging (fMRI) detects local task-related changes in blood oxygenation which very closely follows the neural activity. However, potential artifacts can be introduced into the data from non-descript head movements or movements outside the field of view. Positron emission tomography (PET) uses radioactive tracers to study local changes in brain perfusion ($H_2{}^{15}O$) or glucose metabolism (^{18}F-fluorodeoxyglucose). Problems that emerge using oxygen-15 labelled water include a lack of contrast in the images from its diffusability and a very small imaging window (2 minute half life) (Vaquero and Kinahan, 2015). It’s also possible that the wide variety of swallowing tasks and experimental designs within the tasks can lead to bias in brain areas related to the specific tasks (Söros et al., 2009).

Systematic reviews provide some of the best evidence for medical interventions and their possible uses in clinical settings. A meta-analysis allows statistically significant results to be determined across the results of several studies, meaning a more accurate result can be obtained. Brain-imaging studies are perfect for meta-analyses because their results are typically reported in stereotaxic coordinates that can be transformed into a single stereotaxic image, and a more accurate network of brain structures and networks can be determined. This study used a meta-analysis technique based on activation likelihood estimation (ALE). ALE takes specific activation foci and creates a whole-brain map by assigning voxels values based on the probability that at least one of the points in the data set falls within the localized voxel (Turkeltaub et al., 2002). Meta-analytic connectivity modelling (MACM) was also used to determine co-activation patterns of a seed voxel across a data set of neuroimaging results (Eickhoff et al., 2011). The aim of this meta-analysis was to identify and compare brain activations during healthy, normal swallowing. As well as the functional connectivity and underlying neural networks of the areas activated.

Methods

A systematic and comprehensive search for sources meeting the following criteria was performed: (1) The databases of PubMed and ISI Web of Science were searched; (2) Key phrases and key words used were: whole brain imaging, “functional magnetic imaging”, fMRI, “positron emission tomography”, PET, imaging, swallow, swallowing, deglutition; (3) The references found in the identified articles were searched; (4) Articles citing all identified articles were examined. Additional databases (Google Scholar and PsycInfo) were searched using similar terms for articles. It is important to note that very few stereotaxic imaging studies on healthy swallowing were reported.

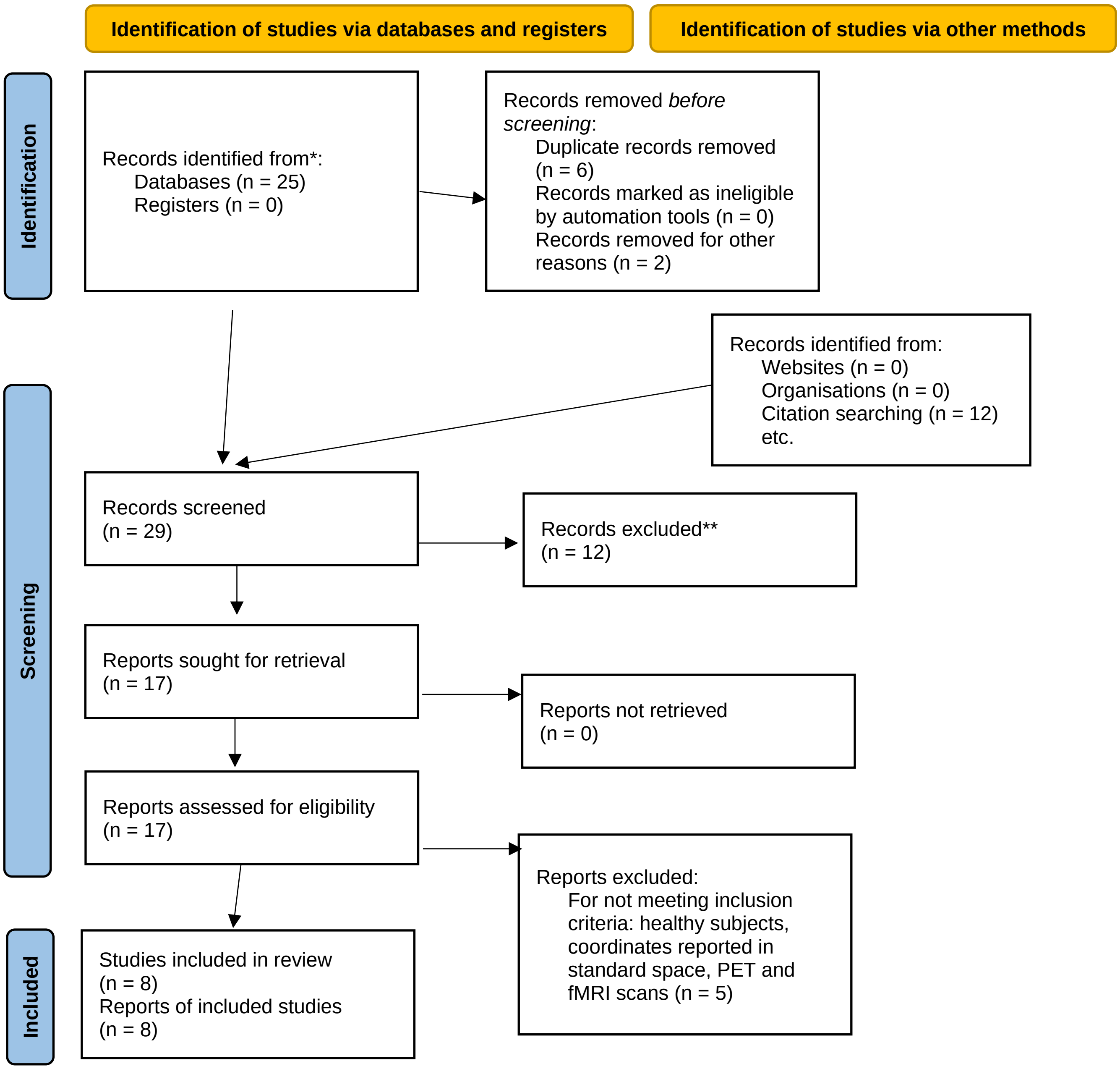

Figure 1: This diagram depicts the inclusion criteria and study selection process.

#	Reference	N	Foci	Contrast Reciprocal	Swallowing Task	Paradigm Class (besides "Swallowing"
1	Fraser et al., 2002	8	8	Water Swallowing > Non-Water Swallowing, Pre-Stimulation	Water Injection	None
			8	Water Swallowing > Non-Water Swallowing, Post-Stimulation		
2	Hamdy et al., 1999	8	9	Swallowing > Rest	Water Infusion	
3	Martin et al., 2007	8	33	Saliva Swallow > Rest	Saliva Swallow, Water Infusion	Flexion/Extension
			24	Water Swallow > Rest		None
			32	Shifted Water Swallow > Rest		
			7	Water Swallow > Saliva Swallow		
			8	Saliva Swallow > Water Swallow		
4	Moon et al., 2016	15	13	Swallow > Rest	Volitional Swallow	None
			6	Healthy Elderly > Healthy Young: Swallow > Rest		
5	Ogura et al., 2012	8	15	Oral Ball-Rolling > Rest	Tongue Roll	Flexion/Extension, Lip Pursing/Tongue Movement
6	Paine et al., 2008		21	Saline Infusion > Rest	Saline/Water Infusion	None
7	Suzuki et al., 2003	11	5	Swallowing > No Swallowing	Volitional Swallow	None
8	Zald & Pardo, 2000	23	22	Water > Rest	Water Injection	Taste, Olfactory Monitor/Discrimination
			21	Water > Swallowing		
			20	Water > Odor Detection		

Table 1: List of the number of participants, number of reported foci, contrast reciprocal, swallowing task, and paradigm class for each reference/contrast.

BrainMap software was used to carry out both the ALE and MACM. BrainMap is a database that archives stereotaxic results from neuroimaging experiments in standard brain space. The BrainMap software used in the following analyses are: Scribe (version 3.6) allows users to submit data and meta-data from selected publications to be reviewed before archival. Sleuth (version 3.0.4) allows users to search for and retrieve stereotaxic and meta-data from publications archived in BrainMap. GingerALE (version 3.0.2) gives users the ability to carry out ALE-based meta-analyses.

ALE

The ALE was carried out using activation coordinates from the included studies (Table 1) and BrainMap's GingerALE software (version 3.0.2). The ALE conducted and reported was based on healthy swallowing in normal adults. This ALE included 8 studies and 16 experiments with 252 foci from 81 subjects. The standardized procedures for performing ALE using the GingerALE user manual were followed (Research Imaging Institute, 2013 https://www.brainmap.org/ale/manual.pdf). For an ALE meta-analysis, a set of coordinates and experimental meta-data (identified as suitable for the research question) are retrieved with

Sleuth. The coordinates are put into GingerALE and smoothed with a Gaussian distribution to account for associated spatial uncertainty (using an estimation of the interstudy and intersubject variability typically seen in neuroimaging studies) (Source). The ALE value is computed estimating convergence across brain images and measures the likelihood of activation at each voxel in the brain. The ALE algorithm also calculates the above-change clustering between experiments (random-effects analysis) rather than between foci (fixed-effects). An ALE value is generated for each voxel before being converted to a p-value for identification of higher scores than empirically-derived null distributions. The consistency of voxel activation can be assessed due to an increased number of studies reporting activated peaks in close proximity to a voxel increasing the ALE value. The cluster-level inference (family-wise error) and the uncorrected p-value used to threshold the ALE image were both set to 0.001 (2,000 permutations) in GingerALE.

MACM

Meta-analytic connectivity modeling (MACM) investigates whole brain coactivation patterns related to a ROI across a range of tasks and provides a measure of functional connectivity during a range of task-constrained states (Langner et al., 2014). Various task paradigms allow for the extraction of functional connectivity networks that represent interacting brain regions to perform specific perceptual, motor, cognitive, and affective functions. The BrainMap database was searched for studies including healthy subjects reporting normal mapping activations existing within the boundaries of a spherical 3-D ROI, regardless of behavioral conditions. The whole brain activation coordinates from selected studies are assessed for convergence with the ALE method before MACM yields a map of significant coactivations showing a task-free meta-analytic model of the region's functional interactions throughout the brain. The MACM approach allows examination of above chance brain region co-activity within a seed region across a diverse set of neuroimaging experiments. The validity of MACM analyses was proven with diffusion tensor imaging (DTI) and connectivity atlases (CocoMac) such that it was demonstrated to be the meta-analytic equivalent of resting-state functional connectivity maps (Laird et al., 2009).

Coordinates of the ten peak activation clusters were identified through the healthy swallowing ALE and used as seeds for the subsequent MACM analysis. The software Mango (Multi-image Analysis GUI, version 4.1 [1531]) was used to create binary NIfTI images of 6 mm spherical radius ROIs as masks around each peak coordinate. A standard MNI brain template (BrainMap MNI 1x1x1 T1 Template.nii) was used to visualize the ROI masks in Mango. Sleuth was used to individually search for each peak ROI using the criteria: 1) Activations: Activations only, 2) Context: Normal Mapping, 3) Subject Diagnosis: Normals, and 4) the corresponding ROI in MNI space. Studies meeting the criteria were downloaded to Sleuth's workspace. The coordinates from the downloaded experiments were analyzed using GingerALE at a p-value $<$ 0.01 and a minimum volume of 250 mm^3.

Network Modeling

Modeling of the network from the MACM analysis was performed using BrainNet Viewer (version 1). To summarize this procedure, a node file with the coordinates of the peak activations and the corresponding ROI number was created in Microsoft Excel (version 16.71) along with an edge file containing the significant and insignificant connections revealed by the MACM. Matlab (version R2023a) was used to convert these files from .xls to .ascii to be used in

BrainNet Viewer. A surface file (BrainMesh_ICBM152_smoothed.nv) along with the node and edge files were loaded into the software before customizing the image presented with multiple views and directionality. Multiple views of the brain were presented to give a better view of the directionality of connections.

Results

The ALE analysis found four significant peak activations in the left and right precentral gyri, relating to the Broadman areas 3, 4, 6, and 43. The right insula was also activated (Broadman's area 13) along with the left declive in the cerebellum. The medial frontal gyrus relating to Broadman's area 6 was activated as well as the medial dorsal nucleus of the thalamus. Lastly, both the left and right dentate of the cerebellum were activated (Table 2, Figure 2).

ROI	Brain Region	x	y	z
1	R Precentral gyrus	58	-4	20
2	R Precentral gyrus	63	-7	20
3	L Precentral gyrus	-56	-4	20
4	L Precentral gyrus	-60	-4	22
5	R Insula	40	-4	5
6	L Declive	-8	-75	-18
7	R Medial frontal gyrus	2	-4	58
8	R Medial dorsal nucleus	2	-20	0
9	R Dentate	19	-64	-22
10	L Dentate	-18	-64	-20

Table 2: High activation likelihood ROI locations and their associated brain regions.

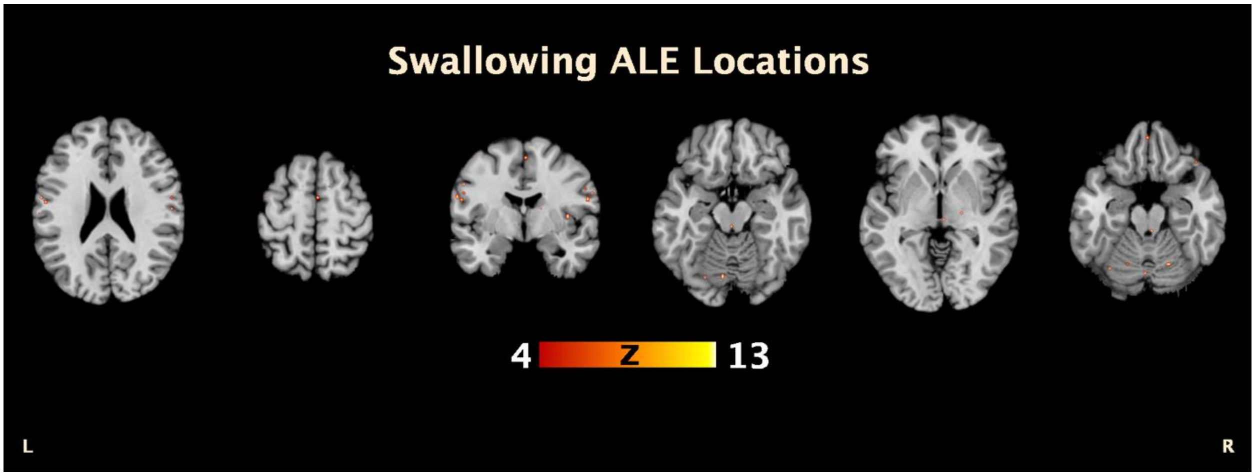

Figure 2: Results from the ALE meta-analysis of healthy swallowing. Voxels with significant activation likelihood are shown in white with less significant activations moving yellow to red.

The MACM found significant one-way connections from the right precentral gyrus to the left declive, medial frontal gyrus, and the medial dorsal nucleus of the thalamus. An additional one-way connection from the left declive to the left dentate was found. Several significant two-way connections were discovered between the first ROI in the right precentral gyrus and the ROIs in the right and left precentral gyri, right insula, medial frontal gyrus, medial dorsal nucleus, and the left and right dentate. Two-way connections from the second ROI in the right precentral gyrus to the other ROIs in the precentral gyri, the right insula, and the left and right dentate of the cerebellum were discovered. The first ROI in the left precentral gyrus was found to have two-way connections to the other ROIs in the precentral gyrus, the right insula, medial frontal gyrus, medial dorsal nucleus, and the left and right dentate. The second ROI in the left precentral gyrus had two-way connections to the other ROIs in the precentral gyri, the medial frontal gyrus, medial dorsal nucleus, and the left and right dentate. Significant two-way connections from the right insula to the two ROIs in the right precentral gyri, the first ROI in the left precentral gyrus, medial frontal gyrus, and the left and right dentate were found. A significant two-way connection between the left declive and the right dentate were also discovered. Significant two-way connections between the medial frontal gyrus and the first ROI of the right precentral gyrus, the two ROIs of the left precentral gyrus, right insula, medial dorsal nucleus, and the left and right dentate were found. Multiple two-way connections between the medial dorsal nucleus and the first ROI of the right precentral gyrus, the two ROIs in the left precentral gyrus, medial frontal gyrus, and the right dentate. The right dentate was found to have two-way connections between the ROIs of the right and left precentral gyri, the right insula, left declive, medial frontal gyrus, medial dorsal nucleus, and the left dentate. Lastly, two-way connections between the left dentate and all the ROIs in the left and right precentral gyri, the right insula, medial frontal gyrus, and the right dentate were discovered (Figure 3 & 4).

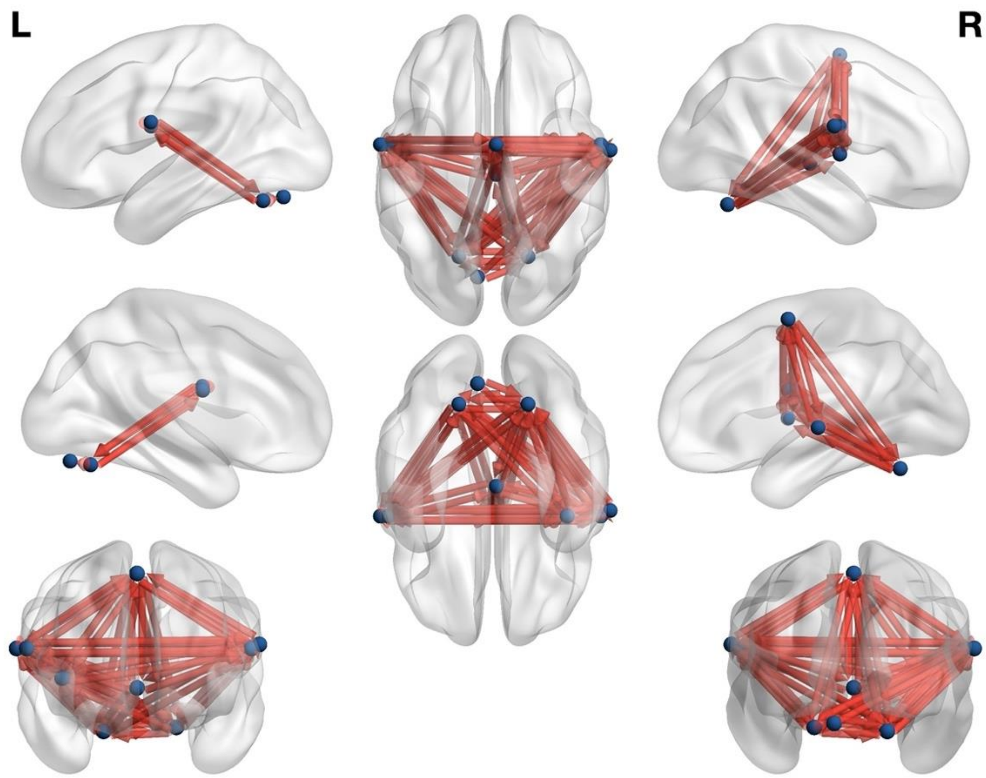

Figure 3: Results from MACM analysis in BrainNet Viewer with directional connections.

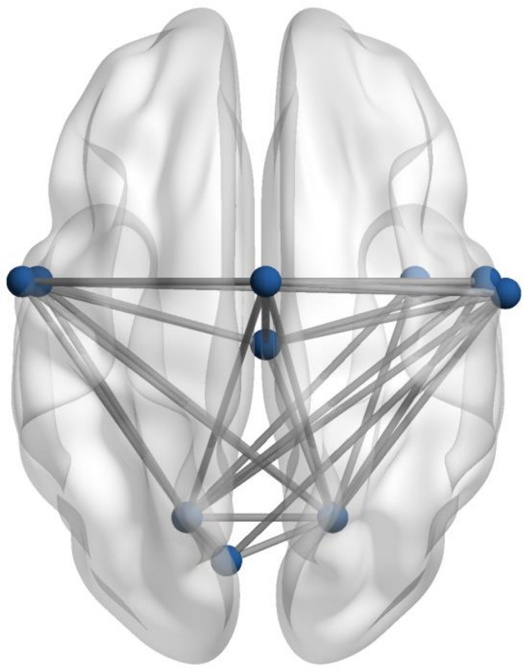

Figure 4: Results from the MACM analysis in BrainNet Viewer without directional connections.

Discussion

ALE

The activations found in the healthy swallowing ALE analysis follow those of previously reported findings. The results from the ALE found significant activations in the left and right precentral gyrus, the right insula, left declive, right medial frontal gyrus, right medial dorsal nucleus, and the left and right dentate nuclei. Congruent to these results, the left precentral gyrus, right insula, and the left culmen (adjacent to the declive of the cerebellum) were found to have significant activations from an ALE meta-analysis on water swallowing (Sörös et al., 2009). Similarly, the right medial frontal gyrus, right insula, left and right precentral gyrus, and the left thalamus were found to have significant activations from another ALE meta-anaysis on saliva swallowing (Sörös et al., 2009). It is important to note that the low yield of healthy swallowing studies may have slightly skewed results and the locations of activations. The discrepancy between activated regions and the lack of activation in the dentate nuclei in other sources could be due to a lack of data in this or other analyses. Here each region's functional significance and relation to swallowing are discussed in comparison to existing literature.

Precentral Gyrus

The activation found in the ALE analysis of the precentral gyri included Broadmann areas 4 and 6, associated with the primary motor cortex and premotor cortex respectively. This activation is supported by a number of other studies who report bilateral activation of the precentral gyri (Malandraki et al., 2009; Martin et al., 2001; Sörös et al., 2009; Zald and Pardo, 1999). The primary motor cortex generates movement-specific signals to be transmitted to the spinal cord and motoneurons for voluntary movements. It has been shown to be involved in the voluntary control of swallowing in awake primates (Martin et al., 1999) and is suggested to control muscle activity in the oropharynx and esophagus during swallowing in humans (Malandraki et al., 2009; Martin et al., 2001, Sörös et al., 2009). The premotor area works in conjunction with the primary motor cortex to help control voluntary movements by processing and then potentiating or depotentiating certain motor plans for execution. Evidence of the role of premotor neurons in the act of swallowing was shown by tracers effective at labeling swallowing motoneurons in a study by Broussard and Altschuler (2000). It was postulated that the premotor cortex is involved in the planning of sequential swallowing movements however the exact function of the cortex in swallowing is still unclear (Malandraki et al., 2009). Thus, previous research confirms the involvement of the precentral gyri and the regions within, adding validity to the multiple significant activations in this area. However, further investigation is required to determine the exact roles of the motor cortices involved in swallowing.

Insula

Significant activation was found in the right insula and more specifically the anterior insula, which is responsible for vibrotactile processing, gustation, olfaction, and emotions like disgust and anxiety (Sörös et al., 2009). The role of the insula in human swallowing was postulated to be due to its important connections to cortical, subcortical, and brainstem sites known to be involved in swallowing (Daniels and Foundas, 1997; Martin et al., 2001). These crucial connections are supported in the MACM analysis as significant two-way connections to the precentral gyri, thalamus, and the cerebellum were observed. Further evidence for the role of the insula in swallowing is the significant percentage of individuals with lesions in the insula having dysphagia (Daniels and Foundas, 1997). The results of the study by Daniels and Foundas (1997) suggest the anterior insula to have connections to the primary and supplementary motor cortices and the ventroposteromedial nucleus of the thalamus involved in oropharyngeal swallowing and that lesions in the anterior insula may disrupt these connections, leading to dysphagia. It has been proposed that collateralization of the anterior insula with gustatory processing occurs in the right hemisphere, meaning gustatory and intraoral sensory information modulate the swallowing process (Zald and Pardo, 1999; Martin et al., 2001). This collateralization is supported with the greater activation of the right insula found in the ALE analysis. However, general inconsistency in the exact insular location activated suggests the need for further investigation and experimentation into the role of the insula in deglutition (Malandraki et al., 2009).

Medial Frontal Gyrus

Significant activation of the medial frontal gyrus related to the supplementary motor area (SMA) was reported in the ALE analysis. Data from previous studies indicates greater activation in the right medial frontal gyrus, correlating with the results from this ALE analysis (Peck et al., 2010; Sasegbon and Hamdy, 2021; Sörös et al., 2009). The SMA has been linked to the initiation and planning of motor control and is known to have connections to the thalamus and other motor cortices as well as the insula (Daniels and Foundas, 1997; Peck et al., 2010; Malandraki et al., 2009). It is proposed that the SMA plays an important role in the control, planning, and execution of swallowing tasks (Malandraki et al., 2009; Peck et al., 2010; Sörös et al., 2009) However, it is yet unclear as to the exact role of the supplementary motor cortex in deglutition and further investigation is necessary to identify this role.

Thalamus

The ALE analysis found a significant activation peak in the medial dorsal nucleus of the thalamus. The thalamus is known to be a relay station for sensory information to travel to higher cortical area with some of its nuclei acting as association areas (Malandraki et al., 2009). Data from previous studies supports the results from this analysis by reporting significant activation in the thalamus (Malandraki et al., 2009; Peck et al., 2010). Most literature on the activation of the thalamus during swallowing struggles to pinpoint specific nuclei, leading to the proposal that the thalamus processes sensory and motor input through cortical and striatal connections and transfers the information to higher cortical structures (Malandraki et al., 2009). Thus, further investigation into the specific nuclei and the medial dorsal nucleus of the thalamus is required to identify specific roles and functions of the nuclei.

Cerebellum

The cerebellum plays an important role in the accuracy, smoothness, and coordination of muscular movements as evidenced by movement behavior in individuals with cerebellar lesions (Sasegbon and Hamdy, 2021). Peak activations from the ALE analysis show bilateral activation of the cerebellum in both dentate nuclei as well as activation in the left declive, indicating these regions play a role in modulating the muscles used in swallowing. Bilateral activation of the cerebellum was also found in several fMRI and PET studies with some indicating greater activation of the left cerebellar hemisphere and therefore supporting the findings of this analysis (Sasegbon and Hamdy, 2021). Data from previous studies suggests activity in the left cerebellar hemisphere most likely represents a specific pharyngeal/esophageal swallowing region and the role of the cerebellum in controlling the coordination, sequencing, and timing of swallowing (Zald and Pardo, 1999). Similarly, the cerebellum has been proposed to be involved in the modulation of pharyngolarygeal muscles and the coordination of sensory input with motor output during the pharyngeal components of swallowing (Maladraki et al., 2009). However, other studies regarding cerebellar lesions have found no significant link between these lesions and dysphagia, suggesting the cerebellum does play a role in swallowing but is not as integral to the circuit as other brain regions like the primary motor cortex and insula. Due to a lack of specificity in reports of activation peaks in cerebellar regions in literature, it is difficult to determine the exact role of the dentate nuclei and the left declive in the swallowing process. Therefore, further investigation into the role of the cerebellar structures in the process of swallowing is required to understand the exact role the cerebellum plays.

Connectivity

The MACM analysis provided significant two-way and one-way connections between the precentral gyri, medial frontal gyrus, insula, medial dorsal nucleus of the thalamus, declive, and dentate nuclei of the cerebellum. Previous studies into cerebello-cortical pathways support these significant connections by indicating communication from the dentate nucleus of the cerebellum to the thalamus before terminating in the primary motor cortex (Sasegbon and Hamdy, 2021; Jayasekeran et al., 2010). Furthermore, the anterior insula is shown to have connections to the primary and supplementary motor cortices, ventroposteromedial nucleus of the thalamus, and the nucleus tractus solitarius which all play a role in swallowing-related activities (Daniels and Foundas, 1997; Sasegbon and Hamdy, 2021). A previous meta-analysis also suggests the thalamus acts as a relay for basal ganglia flow to the supplementary motor area (Sörös et al. 2009). These findings support the significant connections discovered between the precentral gyri, medial frontal gyrus, insula, cerebellum, and thalamus and make sense regarding the functions of these brain regions. The motor cortices of the precentral gyri and medial frontal gyrus control the planning and execution of swallowing through information relayed by the thalamus. The insula and cerebellum play a role in communicating between these regions but while the insula modulates sensory information, the cerebellum modulates some of the muscles involved in the swallowing process to ensure smooth, untroubled deglutition.

Future Research and Applications

Through an understanding of the regions of the brain involved in swallowing, clinicians and neurologists can identify which regions are inactive or not working properly. They then can identify specific treatments to best remedy the deglutition issues present in patients. However, this does not exclude an understanding of the connections between these regions as functional problems in one region can cause issues in others as well. Thus, a thorough understanding of not only the brain regions, but their functional connectivity to each other and other parts of the nervous system is required to give medical professionals the tools they need to reliably treat swallowing disorders.

It is clear that more research into specific brain regions and their relation to swallowing is necessary to understand their roles and their connectivity to other regions. An emphasis on reporting the stereotaxic coordinates of activated regions whenever possible should be placed on studies and experiments using fMRIs, PET scans, or other neuroimaging processes. This would allow better specificity in activated regions as well as open opportunities for further ALE meta-analyses to provide more accurate and actionable results.

Challenges and Limitations

While meta-analyses provide statistically sound quantitative, voxel-wise integration of neuroimaging data, the ALE approach has methodological limitations. Particularly it does not take the number of subjects or reported activation foci in single studies into account. It also does not allow the usage of studies reporting results in anything other than stereotaxic coordinates. The MACM approach also has its own limitations with frequency bias. If a given voxel is frequently activated in the databased experiments, it is more likely to co-activate with any given seed region (Langner et al., 2014). This bias may lead to more significant co-activations in regions that may otherwise be less significant.

The lack of studies reporting stereotaxic coordinates of activations during the course of swallowing may have led to slightly inaccurate or skewed peak activations during the ALE analysis which may have in turn affected the results of the MACM analysis. However, meta-analyses containing a similar number of studies successfully employed the ALE approach and were supported by previous and future research in swallowing (Sörös et al., 2009). This as well as the literature supporting the results of the ALE analysis installs confidence into the results of this meta-analysis.

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