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Brain Activation during the Voiding phase of Micturition in Healthy Adults: A Meta-analysis of Neuroimaging Studies

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Abstract

Introduction: Several studies have used a variety of neuroimaging techniques to measure brain activity during the voiding phase of micturition. However, there is a lack of consensus on which regions of the brain are activated during voiding. The aim of this meta-analysis is to identify the brain regions that are consistently activated during voiding in healthy adults across different studies.

Materials and Methods: We searched the literature for neuroimaging studies that reported brain coordinates that were activated during voiding. We excluded studies that reported coordinates only for bladder filling, during pelvic floor contraction only, and studies that focused on abnormal bladder states such as neurogenic bladder. We used the activation likelihood estimation (ALE) approach to create a statistical map of the brain and identify the brain coordinates that were activated across different studies.

Results: We identified 9 studies that reported brain activation during the task of voiding in 91 healthy subjects. Together, these studies reported 117 foci for ALE analysis. Our activation likelihood estimation map yielded six clusters of activation in the pons, cerebellum, insula, anterior cingulate cortex, thalamus, and the inferior frontal gyrus.

Conclusions: Regions of the brain involved in executive control (frontal cortex), interoception (anterior cingulate cortex, insula), motor control (cerebellum, thalamus), and brainstem (pons) are involved in micturition. This analysis provides insight into the supraspinal control of voiding in healthy adults and provides a framework to understand dysfunctional voiding.

Keywords

brain; functional neuroimaging; urination; meta-analysis; urinary bladder; neurogenic bladder

Introduction

Micturition consists of two phases: the storage and voiding of urine. Underactive bladder is a common voiding dysfunction in which the detrusor muscle is unable to generate an effective contraction sufficient to empty the bladder (Osman and Chapple, 2014). As many as 9–48% of men and 12–45% of women undergoing evaluation for lower urinary tract symptoms are diagnosed with underactive bladder (Abarbanel and Marcus, 2007; Nitti et al., 2002; Resnick et al., 1996). Though underactive bladder causes distressing lower urinary tract symptoms and has serious consequences such as recurrent urinary tract infections and need for prolonged catheterization, the underlying cause of underactive bladder remains known.

Leading theories suggest that the failure of the bladder to generate a sufficient bladder contraction during the voiding phase is likely due to an underlying neurologic mechanism (Osman and Chapple, 2014). Evidence from animal experiments suggests that during the voiding phase regions in the caudal brainstem coordinate the contraction of the detrusor muscle with the relaxation of the urethral sphincter but the initiation of micturition is determined in regions of the forebrain (Holstege et al., 1986). In humans, several neuroimaging studies have been performed to determine central mechanisms of micturition. Using activation likelihood estimation method (ALE), Arya et al., performed a meta-analysis of the regions of the brain that are activated during the storage phase of micturition (Arya et al., 2017). Such studies have allowed the development of a model of central control of bladder filling in humans such that afferent signals from the bladder ascend in the spinal cord and synapse in the PAG. Afferent signals from the PAG are relayed via the thalamus to the insula, and likely the ACC which ultimately allows storage of urine in the bladder through increased sympathetic discharge, relaxation of the detrusor muscle of the bladder and contraction of urethral sphincter (Griffiths and Fowler, 2013; Arya et al., 2017). However, a similar meta-analysis that integrates the findings of neuroimaging studies performed in the voiding phase has not been performed. An understanding of the regions of the brain that are activated during voiding would allow clinicians and researchers to determine which areas of the brain should be targeted in the treatment of underactive bladder.

In recent years, activation likelihood estimation (ALE) has emerged as an important approach for synthesizing neuroimaging data. Rather than simply counting which areas of the brain are activated, ALE analysis incorporates the actual brain coordinates to determine the probability of brain regions that have been activated during a “task” such as voiding of urine (Eickhoff et al., 2009; Eickhoff et al., 2012). Using ALE, prior studies have identified brain regions involved in storage of urine (Arya et al., 2017), irritable bowel syndrome (Tillisch et al., 2011), sleep deprivation (Ma et al., 2015), and depression (Fitzgerald et al., 2008). The aim of our study was to perform an ALE meta-analysis of neuroimaging studies to identify areas of the brain that are activated during the voiding phase of micturition in healthy adults using various neuroimaging techniques with different experimental designs.

Materials and Methods

We searched the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed/>) for neuroimaging studies published until January 2016 that investigated the regions of the brain where activity increases during voiding in humans. The keywords used for the search included “voiding” and “micturition” and were each combined with the terms “neuroimaging,” “fMRI,” and “PET” to identify pertinent studies. Study abstracts from the search results were reviewed to identify relevant studies, and the bibliographies of the included studies were reviewed to ensure completeness. Inclusion criteria of this meta-analysis were studies that published the coordinates of brain regions where activity increases during voiding (i.e., activation) and studies whose subjects voided as part of the imaging protocol. We excluded studies that: (1) focused on the task of bladder filling (i.e., storage) only and not voiding, (2) investigated pelvic floor muscle contraction/relaxation only, and (3) studied subjects with lower urinary tract dysfunction or neurogenic bladder. The PRISMA flow diagram is shown in Table 1 (Moher et al., 2009).

All brain coordinates published in the included studies were reviewed and the relevant coordinates were abstracted. Coordinates not pertaining to voiding or coordinates derived from subjects who could not successfully void during the study protocol were excluded. The timing of imaging for each study in relationship to the voiding protocol was carefully reviewed for each study to determine whether imaging was performed at the “initiation” of micturition or during actual micturition.

The activation likelihood estimation (ALE) meta-analysis was conducted using GingerALE 2.3 software. The mathematical algorithms underlying ALE have been previously reported (Eickhoff et al., 2009; Eickhoff et al., 2012; Turkeltaub et al., 2012). All coordinates published in MNI space were transferred into Talairach space using the Lancaster transformation (Lancaster et al., 2007). Then, using the imputed coordinates, the software generated a whole-brain statistical map estimating the likelihood of activation of each voxel. We treated each focus as a probability distribution centered about a peak at the reported coordinate. The likelihood of activation at a voxel was modelled as the peak of a 3-D Gaussian distribution with subject-based full-width at half-maximum values. The ALE statistic, representing the probability that at least one of the activation foci lies within a given voxel, was calculated at each voxel. This computation was repeated at each voxel in the brain to generate a ALE map. Subsequently, using a significance threshold set at < 0.05 , the whole brain statistical map was thresholded and tested using a nonparametric permutation test developed by Nichols and Holmes (Nichols and Holmes, 2002). We tested the null hypothesis that activation foci are spread uniformly throughout the brain (i.e., clustering of coordinates is random). Multiple comparisons were corrected at the cluster level and 1,000 permutations were allowed for calculation of the ALE statistical map.

We performed separate coordinate based meta-analyses for all subjects combined, male subjects, female subjects, subjects who voided successfully in the scanner, and subjects who could not void in the scanner. We then performed a contrast analysis to investigate differences in brain regional activation in males versus females, and for subjects who voided

in the scanner versus those who could not void in the scanner. The contrast analysis was also performed using GingerALE 2.3.1.

Results

Based on the search described above and subsequent application of inclusion and exclusion criteria, we identified 9 studies that measured regions of the brain activated during the voiding phase of micturition (Table 2). Of these, three studies used PET scan, one used SPECT, and five used fMRI scanning. A review of the voiding protocols showed that in the majority of the studies a transurethral catheter was not placed; however, in three studies subjects voided around a catheter (Nour et al., 2000; Krhut et al., 2012; Shy et al., 2014). All studies measured brain activation during the initiation of micturition while one study also compared the initiation of micturition to actual micturition (Michels et al., 2014). Only two studies reported brain deactivation (Blok et al., 1997; Blok et al., 1998).

The nine studies were comprised of a total of 115 subjects. Of these, 91 subjects (54 men and 37 women) successfully voided during neuroimaging while 24 subjects were unable to void in the scanner. Aggregately, the 91 subjects who voided in the scanner yielded 117 foci of brain activation during voiding.

The ALE meta-analysis revealed six clusters (i.e., groups of voxels) where brain activity increased during voiding (Table 3). These clusters corresponded to brain regions in the brainstem (pons), cerebellum, thalamus, insula, anterior cingulate cortex, and inferior frontal gyrus (Figure 1).

Analysis the 54 male subjects who voided in the scanner did not identify any cluster of activation. However, analysis of the female subjects identified a cluster in the cerebellum and the anterior cingulate cortex. Three studies reported coordinates of subjects who were unable to void in the scanner (Blok et al., 97, Block et al., 98, and Michels et al., 2014). Meta-analysis of these 22 subjects identified a cluster of activation in the pons ($x = 10$, $y = -28$, $z = -34$).

Discussion

Using ALE meta-analysis, Arya et al., (2017) reported on the regions of the brain that are activated during the filling or the storage phase of micturition. The present study provides the first voxel based meta-analysis to identify brain regions that are activated during the voiding phase of micturition. These regions include the brainstem, inferior frontal gyrus, insula, anterior cingulate cortex, thalamus, and cerebellum.

Our finding that the anterior cingulate cortex (ACC) and the insula are activated in the voiding phase of micturition is clinically important. The ACC and the insula are also activated during bladder filling both in healthy controls as well as in subjects with overactive bladder, a condition of urinary urgency with or without incontinence (Griffiths et al., 2007, Komesu et al., 2011). The insula, an area of the cerebral cortex that lies deep to the lateral sulcus receives afferent homeostatic information from the viscera, such as heart rate, respiration, digestive processes and micturition (Craig, 2002). Also called the sensory cortex

of the autonomic nervous system, activation of the insula during the storage phase represents afferent signaling from the bladder to the CNS. The ACC, located on the medial surface of the frontal lobe and surrounding the anterior genu of the corpus callosum, is called the motor cortex of the autonomic nervous system because it is responsible for emotional, behavioral, and motor responses to visceral stimuli (Bush et al., 2000). In the case of the bladder, ACC activation results in increased thoracolumbar sympathetic discharge that causes detrusor relaxation and urethral sphincteric contraction (de Groat et al., 2015). During the storage phase, ACC activation occurs when there is a strong sense of urgency indicating a motor response to threatened loss of urine (Griffiths and Fowler, 2013). The role of the ACC during voiding is less clear. Activation of the insula and the ACC during the voiding phase may indicate that afferent signaling to the brain is important for the initiation of voiding. Alternatively, activation of the ACC and the insula during voiding may represent tight coupling between afferent and efferent centers in the brain.

In our meta-analysis, a cluster of activation emerged in the ACC in female subjects despite a relatively small sample size. This finding suggests that the ACC, a region of the brain that is involved in contraction of the pelvic floor muscles that serve as the external urethral sphincter, plays a particularly important role in voiding in women. Fowler's syndrome is a distressing condition of unexplained retention of urine that occurs in young women and is associated with a poorly relaxing urethral sphincter (Osman and Chapple, 2014). Given the ACC's role in pelvic floor contraction, abnormal activation of the ACC during voiding could potentially contribute to Fowler's syndrome. Using arterial spin labeling, a neuroimaging technique that allows quantitative measurement of cerebral blood flow, Arya et al., (2017) demonstrated increased blood flow to the ACC in women with overactive bladder. Future studies including similar neuroimaging techniques could potentially help to elucidate the pathogenesis of dysfunctional voiding.

We noted activation of the inferior frontal gyrus in the medial prefrontal cortex (PFC) during the voiding phase. Activation of the PFC has been reported both in subjects who could void successfully as well as those who were unable to void in the scanner despite trying vigorously to do so (Blok et al., 1997; Blok et al., 1998; Michels et al., 2015). These findings suggest that the decision to void is likely generated in the PFC. The prefrontal cortex is part of the attention network and is also concerned with the highest level of brain function including executive decision making (Rossi et al., 2009). However, the PFC is not an isolated decision center. Animal experiments show that the PFC has extensive connections to the periaqueductal gray (PAG), a region in the mid-brain that is integral to both storage and voiding (Noto et al., 1991). Most of the time, the bladder is in the storage phase and the role of the PFC is to inhibit the PAG. When the afferent signals to the PAG exceed a certain threshold, they are sent to the PFC to determine if voiding is safe and appropriate (Griffiths and Fowler, 2013). If the PFC determines that it is desirable and socially appropriate to do so, the inhibition of the PFC on the PAG is lifted resulting in activation of the PMC and voiding.

Though our meta-analysis did not identify a region of activation in the midbrain, we noted a distinct cluster of activation in the pons in subjects who successfully voided in the scanner (6, -30, -24) as well as those who could not void in the scanner despite vigorously trying to

do so (10, -28, -34). In animal experiments, excitation of a group of cells in the dorsolateral pons results in detrusor contraction and has been called the pontine micturition center (PMC) or the Barrington's nucleus or the M region (Blok and Holstege, 1997). On the other hand, stimulation of a group of cells situated more ventrally and laterally in the dorsal pontine tegmentum results in contraction of the pelvic floor including the urethral sphincter through the Onuf's nucleus in the sacral spinal cord and has been called the L-region or the continence center (Holstege et al., 1986). In our meta-analysis, even though the cluster of activation in the pons in successful voiders is dorsal to the cluster activated in unsuccessful voiders, we cannot reliably determine whether these clusters represent the pontine micturition and continence centers respectively. The brainstem is difficult to visualize on neuroimaging studies and the precise location of the micturition and continence centers in humans remains unclear.

We also noted activation of the thalamus during the voiding phase. The thalamus is a complex of nuclei surrounded by the cerebral hemispheres and has an important role in both sensory and motor pathways for integrating somatosensory information (Herrero et al., 2002). As part of the attention and awareness networks, thalamic activation during storage determines which afferent signals from the bladder should reach the cerebral cortex (Arya, 2017). During voiding, thalamic activation may represent the central role of the thalamus in coordinating the integration of the decision to void generated in the PFC with the relaxation of the pelvic floor including the external urethral sphincter muscles.

Our meta-analysis identified an area of activation in the cerebellum during the voiding phase. Arya et al., reported significant activation of the cerebellum in the pyramid during storage also (Arya et al., 2016). Animal studies have demonstrated extensive connections of the cerebellum to other parts of the central nervous system including those involved in micturition and lesions of the cerebellum in humans are associated with both storage and voiding symptoms (Sakakibara et al., 2004). The cerebellum has important roles in motor control and may serve as a modulatory center for coordinating detrusor contraction with the relaxation of the external urethral sphincter during voiding and vice versa during the storage of urine.

The findings of our study allow us to develop a supraspinal model of voiding that validates existing models developed from animal studies. During storage, the PMC is under the inhibitory influence of the PFC and this increases sympathetic discharge which relaxes the detrusor muscle of the bladder and contracts the external urethral sphincter. With bladder filling, when afferent signals from the bladder to the insula and ACC reach a certain limit, signals are conveyed to the frontal cortex. If voiding is socially appropriate, the PFC lifts its inhibitory influence on the PMC in the brainstem, likely through the PAG, allowing increased parasympathetic activity and detrusor contraction. Under the modulatory influence of the thalamus and the cerebellum, detrusor contraction is coordinated with external urethral sphincter relaxation allowing voiding to proceed.

Our study has several limitations. These include relatively small sample size, heterogeneity of neuroimaging techniques, and differences in voiding protocols. Our small sample size did not allow us to investigate differences in brain activation between male and female subjects,

successful versus unsuccessful voiders, and the initiation versus the maintenance phase of voiding. Electrophysiological studies in cats suggest that initiation of the bulbospinal micturition reflex requires activation of several regions of the brain, but that once initiated, micturition continues automatically with minimal supraspinal input (de Groat and Wickens, 2013). However, since only one study reported on the coordinates activated during the maintenance phase (Michels et al., 2015), we were unable to perform a contrast analysis of brain activations during initiation of voiding and maintenance. Similarly, our analysis of the three studies who reported brain activation in “unsuccessful voiders” revealed only one cluster in the pons; additional areas are likely involved in voiding dysfunction. In spite of these limitations, our meta-analysis allowed us to integrate the findings of existing studies and develop a supraspinal model for voiding that identifies key regions of the brain that could potentially be targeted in the diagnosis and treatment of dysfunctional voiding.

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Figure 1.

Areas of the brain activated during voiding: results of a meta-analysis using brain coordinates of 115 subjects from nine studies. (A) Anterior cingulate cortex and cerebellum (B) Insula, inferior frontal gyrus, and thalamus (C) Pons and cerebellum.

Table 1.

PRISMA flow diagram of studies of voiding phase of micturition in healthy adults.

Table 2.

Studies included in the meta-analysis of brain activations during bladder filling

First author, Year	Imaging modality	Subjects (N, sex)	Subjects' age mean (range) years
Fukuyama, 1996	SPECT	10 males, 10 voided	28.2 $\pm$ 5.6 (22–37)
Blok, 1997	PET	17 males, 10 voided in scanner	32 (20–50)
Blok, 1998	PET	18 females, 10 voided in scanner	27 (20–51)
Nour, 2000	PET	12 males, 8 voided	23.4 $\pm$ 1.1 (22–25)
Seseke, 2006	fMRI	11 females, all “imitated” voiding	30 $\pm$ 6.9 (20–44)
Seseke, 2008	fMRI	12 males, all “imitated” voiding	32.4 $\pm$ 7.9, (19–49)
Krhut, 2012	fMRI	12 females, 6 voided in scanner	49.6 $\pm$ 17 (20–68)
Shy, 2014	fMRI	13 females, 10 voided in scanner	32.4 (25–45)
Michels, 2014	fMRI	22 males, 14 voided in scanner	26.4 $\pm$ 6.2 (18–45)

Table 3:

Regions of the brain activated during voiding from a meta-analysis of nine studies

Cluster	Region of interest	Volume (mm3)	x	y	z	ALE value
1	Cerebellum	1752	12	-44	-28	0.01285
2	Anterior Insula	1568	-34	22	2	0.01644
3	Thalamus	1472	-4	-6	-8	0.01384
4	Pons	1160	6	-30	-24	0.00854
5	Anterior cingulate cortex	904	14	36	10	0.01667
6	Inferior frontal gyrus	840	58	20	-4	0.01377

x, y, z: coordinates in standard stereotaxic space in millimeters for the maximally significant voxel where x is the lateral displacement from the midline, y is the anterior-posterior displacement relative to the anterior commissure, z is the vertical displacement relative to the anterior-posterior commissure line

ALE: Activation likelihood estimation