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Original Article

Influence of visual and auditory cues about bladder volume on real-time filling sensation in healthy volunteers

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Abstract: Auditory/visual (A/V) cues can trigger urgency in some individuals with overactive bladder (OAB), and patient-reported bladder sensation can be characterized during non-invasive oral hydration studies. The aim of this investigation was to test the hypothesis that A/V cues of bladder volume can alter patient-perceived bladder sensation during hydration studies. Healthy volunteers without urinary symptoms based on ICIq-OAB survey scores were recruited for an oral hydration study where they completed two fill/void cycles. The study was repeated twice, one week apart. Throughout bladder filling, participants reported real-time sensation (0-100%) using a Sensation Meter, and bladder volumes were measured at 5 min intervals with both 3D ultrasound and BladderScan®. Participants were divided into a Cues(+) group that was allowed to view their ultrasound images and hear volume measurements of the BladderScan® every 5 min and a Cues(-) group that was not exposed to these A/V cues. The A/V Cues(+) group had 10 participants (5 women and 5 men) and the Cues(-) group had 10 participants (7 women and 3 men). During the second visit, the Cues(+) group demonstrated decreased sensation compared to the Cues(-) group in the slower first fill, but not the faster second fill. The results of this study demonstrate that A/V cues about bladder volume can acutely alter sensation during hydration studies in healthy individuals with normal bladder function.

Keywords: Lower urinary tract symptoms, overactive bladder, sensation, ultrasound, urinary bladder

Introduction

Urinary urgency is defined as "the complaint of a sudden compelling desire to pass urine, which is difficult to delay", and overactive bladder (OAB) is defined as "urgency, with or without urge incontinence, usually with frequency and nocturia", [1]. OAB syndrome is highly prevalent [2, 3], increases with age in both sexes, and has a negative effect on quality of life [4]. However, a major challenge in OAB research has been the lack of objective metrics to characterize bladder sensation. This likely stems from the highly complex nature of bladder sensation in that the increasing awareness of bladder fullness during filling involves the interplay of many systems including the lower urinary tract, spinal cord, brain stem, and cerebral cortex [5].

Recently, there has been significant interest in quantifying bladder sensation throughout filling [6-11], and a novel Sensation Meter has been developed to help characterize real-time bladder sensation during standard urodynamics testing [12] and during non-invasive oral hydration studies [10, 13, 14]. This Sensation Meter represents a major advance from previous methods used to assess OAB, including validated surveys and void diaries which are subject to recall bias and are difficult to standardize. In addition, verbal sensory thresholds of first sensation, first desire, and strong desire used in urodynamics [1, 15] are episodic and can be highly influenced by invasive urethral catheters and by investigator prompting [16, 17]. However, validation of this Sensation Meter will require detailed studies to explore factors that influence bladder sensation [18].

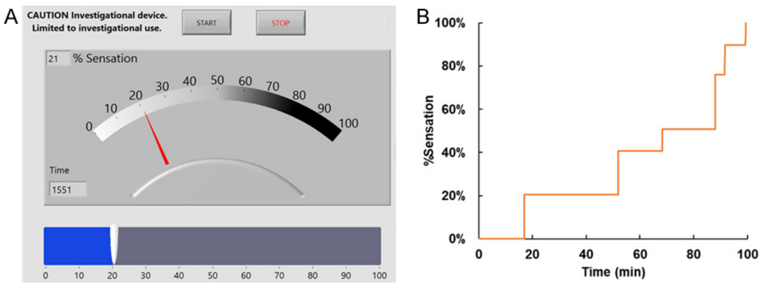

Figure 1. A. The Sensation Meter with the slider bar participant interface (bottom) and graphical display of bladder fullness sensation from 0 to 100% (middle). B. Example Sensation Meter data for a participant that reported 6 increases in sensation during 100 min of natural filling.

One important area of research in bladder sensation is how environmental cues, such as the audio/visual cue of seeing and hearing running water, can provide a stimulus to trigger acute increases in bladder sensation in some individuals [19-22]. Indeed, humans may develop conditioned associations that lead to dramatic increases in bladder sensation, urinary urgency, and even urge incontinence. Examples of these conditioned associations include "latchkey" incontinence [19] or hearing the sound of running water [20]. The etiology of latchkey incontinence, in which urinary incontinence is triggered by placing a key into the front door lock, is not known. Investigators have successfully used running water sounds to help prostate surgery patients to urinate [23]. Another study found that the sound of running water from a mobile phone application helped subjects with lower urinary tract symptoms increase their peak flow rates [24]. Furthermore, it is well-established that distraction techniques used in behavioral therapy can decrease bladder sensation [25, 26]. These techniques can include visual distractors, such as solving a puzzle or playing a game on a computer, and verbal/auditory distractors, such as reciting a poem or counting [27]. Together, these studies highlight the potential effects of auditory/visual (A/V) cues on bladder sensation.

Therefore, the purpose of the current investigation was to test the hypothesis that A/V cues about bladder volume affect real-time bladder sensation during a non-invasive oral hydration protocol. This study will contribute to the validation of an oral hydration protocol using a Sensation Meter and provide insight into sensory modulation as a potential treatment for OAB [25, 28].

Material and methods

This prospective bladder sensation study was approved by the Institutional Review Board. Informed consent was obtained from healthy volunteers (Approval #: IRB HM-20000453). To be included in the study, participants were required to be at least 21 years of age, not pregnant and have no cognitive impairment or known bladder dysfunction. All volunteers completed the validated International Consultation on Incontinence OAB questionnaire (ICIq-OAB) [29] to assess urgency, frequency, urge incontinence and nocturia. Individuals without symptoms of urinary urgency based on a score 0 (never) on question 5a ("Do you have to rush to the toilet to urinate"? With answer choices 0= never, 1= occasionally, 2= sometimes, 3= most of the time and 4= all of the time) and ≤1 on all other questions (frequency, urge incontinence and nocturia) were prospectively enrolled in an oral hydration study based on previously published methodology [10, 13, 14]. Participant information including age, sex, body mass index (BMI), prescription medications, and medical history were recorded.

Protocol visits and training

Participants completed the identical protocol on two separate visits (Visits A and B), one week apart at the same time of day and after consumption of similar foods and beverages based on a food and beverage diary, based on a previous study [14]. All participants received standardized instruction on the Sensation Meter (**Figure 1**) and protocol by clicking through a PowerPoint presentation at the beginning of Visit A. For this investigation, Visit A was considered "untrained" and Visit B was considered "trained" because they had gone through the complete protocol one time [14].

Oral hydration

Oral hydration studies are used to measure subject-reported responses (such as bladder fullness sensation) and/or physiological parameters (such as voided volume) during natural diuresis due to fluid consumption [10, 13, 14].

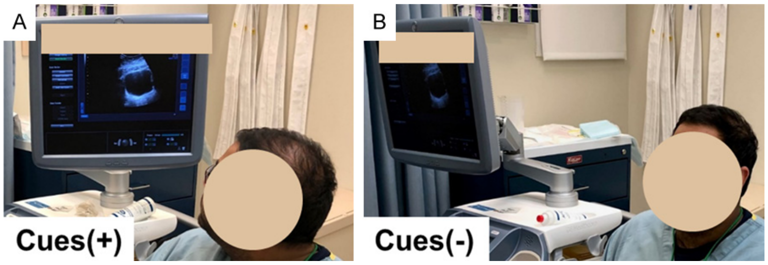

Figure 2. Photos of the experimental setup. Participants were divided into groups with and without auditory/visual (A/V) cues about their bladder volume. A Cues(+) group was allowed to see the bladder ultrasound (US) images and hear communication of their US bladder volumes at 5 min intervals throughout filling (A), and a Cues(-) group was not allowed to see the US bladder images or hear communication of their US bladder volumes (B).

For the current hydration protocol, participants voided in a private bathroom and bladder emptying was confirmed using BladderScan®, Then, participants completed a documented accelerated hydration protocol [13, 14] by consuming 2L Gatorade G2® as rapidly as possible and subsequently completed two successive fill and void cycles. With each void, volumes were recorded and residual volumes measured. Throughout filling, real-time bladder volumes were measured every 5 min with BladderScan® (BVI 9400 System, Verathon Inc., Bothell, WA), and the average of three successive scans was recorded to improve accuracy [30] and used for the construction of sensation-capacity curves [10]. Bladder volumes were also measured every 5 min using 3D ultrasound with a Voluson E8 system and a 4-8 MHz abdominal transducer (GE Healthcare, Zipf, Austria), and these data were used for a separate investigation of bladder shape [31].

Sensation Meter

From the onset of hydration, participants recorded bladder sensation using the Sensation Meter [10, 13, 14] from 0% (bladder empty) to 100% (complete bladder fullness) (**Figure 1**). Continuous real-time sensation was recorded during two successive fill and void cycles and used to generate sensation-capacity curves [10, 14]. The study did not involve prompting. When participants reached 100% sensation, they were escorted to a nearby private bathroom where they could void into a container for measuring voided volume.

A/V cues

In the Cues(+) group, participants were allowed to view their 3D ultrasound images and hear 3D ultrasound and BladderScan® volumes throughout the course of both study visits [14]. In this group, the ultrasound monitor was positioned at an angle that was easily seen by the participant who was seated in chair and both the 3D ultrasound and BladderScan® volume measurements were spoken out loud by the technician and recorded by separate study personnel (**Figure 2A**). However, for the blinded Cues(-) group, the angle of the ultrasound monitor was changed so that the participant was not permitted to see the images, and all bladder volume information was recorded silently (**Figure 2B**). Participants were not aware of blinding status as the studies were done sequentially (unblinded, followed by blinded).

Data analysis and statistics

A previous study demonstrated a training effect during the first fill-void cycle using the Sensation Meter [14]. To avoid the effect of training, the present study focused on analysis of data from Visit B. The capacity for each fill and void cycle was calculated as the final voided volume plus any post-void residual, and average fill rates were calculated as capacity/fill duration. Since diuresis is not always at a constant rate, BladderScan® volumes were fitted to a second order polynomial function of time to provide an improved estimate of bladder volume throughout each fill [14]. Sensation-capacity curves were generated at 5% capacity increments for each fill. Sensation-capacity curves were compared by using area under the curve (AUC) analysis via the trapezoidal rule for specific percent capacity ranges. A threshold AUC value was optimized for each capacity range to distinguish between the groups using an iterative process. Data are presented as mean ± standard error. Statistical comparisons were performed with Student's t test for continuous variables or Fisher's exact test for categorical variables. Differences were considered to have significance if the *P*-value was less than 0.05.

Results

Twenty healthy volunteers were prospectively enrolled in the oral hydration study, with 10 par-

Table 1. Participant groups and characteristics

Participant Groups	Cues(+)	Cues(-)	*p* value
Participants	10	10	
Women	5	7	
Men	5	3	
Age (years)	23.0±0.7	25.6±2.2	0.28
BMI (kg/m^2)	23.8±1.5	24.8.0±1.8	0.67

BMI = Body Mass Index, Cues(+) = group that was allowed to see bladder images and hear bladder volumes during filling, Cues(-) = group was not allowed to see bladder images or hear bladder volumes during filling.

ticipants each in the Cues(+) and Cues(-) groups. No participants had any medical conditions or were on any prescriptions medications that could affect bladder function. There were no differences in age or BMI between the Cues(+) and Cues(-) participant groups as shown in **Table 1**.

Bladder capacities were not different between the Cues(+) and Cues(-) groups for either Fill1 or Fill2 (**Figure 3A**). Average fill rates were significantly greater for Fill2 compared to Fill1 for both the Cues(+) and Cues(-) groups (**Figure 3B**, P=0.004 and P=0.001, respectively).

Figure 4 shows %sensation-%capacity curves for the Cues(+) and Cues(-) groups for Fill1 and Fill2. Analyzed as a categorical variable, AUC for 10/10 Cues(+) and 5/10 Cues(-) were below a threshold of 68.5 AUC between 65% and 85% capacity for Fill1 (**Figure 4A**, green shaded area, Fisher's exact test, P=0.039), but not Fill2 (**Figure 4B**, P>0.05). Based on analysis of AUC as a continuous variable, the Cues(+) group demonstrated a significant decrease in sensation compared to the Cues(-) group between 75% and 85% capacity in Fill1 (**Figure 4A**, denoted by *, P=0.047), but not in Fill2 (P>0.05). A post-hoc power analysis for the comparison between groups based on AUC as a categorical variable yielded a power of 0.83.

Discussion

The current study demonstrates that A/V cues of bladder volume may affect bladder sensation during non-invasive oral hydration. More specifically, exposure to images and volume measures of one's own bladder caused a decrease (right shift) in sensation at higher capacities (65-85%). For example, at 80% capacity, individuals that were not exposed to bladder cues had 86% sensation and those that were exposed to cues has 68% sensation (P<0.05), a sensation decrease of 18%. The clinical significance of this finding is that A/V cues result in sensory modulation, even in healthy individuals with normal voiding function. We hypothesize that A/V cues may have more pronounced effects in individuals with OAB based on previous studies demonstrating that urinary urgency can be triggered by A/V stimuli such as the sound/sight of running water [20, 32].

Overall, it is estimated that approximately 60% of individuals with OAB will experience some form of urgency cue [22, 33], and environmental and situational cues can acutely increase sensation [19]. In patients with OAB, Victor et al. found that increased urgency was associated with cold weather (76%), opening the front door (71%), and hearing running water (42%), being worried (28%), and being tired (6%) [20]. Ghei et al. [19], administered a computer-based survey to patients attending a clinic for OAB and identified five broad categories which provoke urgency including Waking/Rising Urgency, Latchkey Urgency, Running Water Urgency, Cold Urgency, and Mood Urgency. Other investigators found that exposure to the sound of running water as played on a mobile phone app during office-based uroflowmetry resulted in significantly higher urinary flow rates [24]. Additional situational stimuli including ambient cold temperatures [34] and fatigue [35] are also associated with increased lower urinary tract symptoms. Furthermore, during a urodynamics investigation, Erdem et al. demonstrated that a majority of patients experienced first sensation and first desire, simply with sham filling in the setting of investigator prompting [17].

These background studies support our current investigation and illustrate the use A/V cues as mechanisms for bladder sensory modulation. In most of these studies, environmental and situational cues resulted in acute increases in sensation. However, in our study, the exposure of patients to A/V cues of their own bladder volumes resulted in decreased sensation. This finding is supported by prior studies in which biofeedback and other forms of behavioral therapy are used to treat patients with OAB [25]. Furthermore, Clarkson et al. showed that "safe" cues reduced bladder sensation in

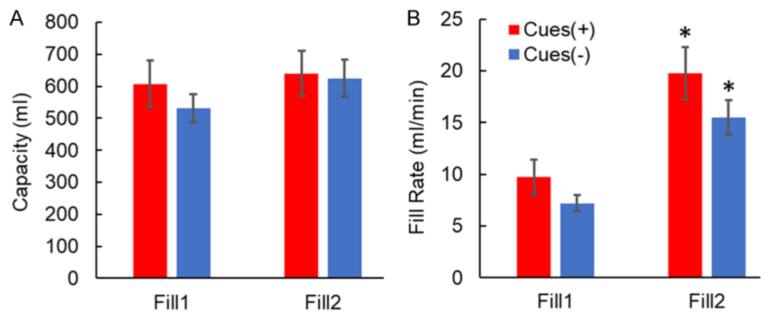

Figure 3. Bladder capacities (A) and fill rates (B) for Visit B. (A) Bladder capacities were not different when comparing the Cues(+) group (red) with the Cues(-) group (blue) or Fill1 with Fill2 (n=10/group, P>0.05). (B) Fill2 was faster than Fill1 for both groups (*, red vs red & blue vs blue, n=10, P<0.05). Fill rates for the Cues(+) & Cues(-) groups were not significantly different (red vs blue for each fill, P>0.05).

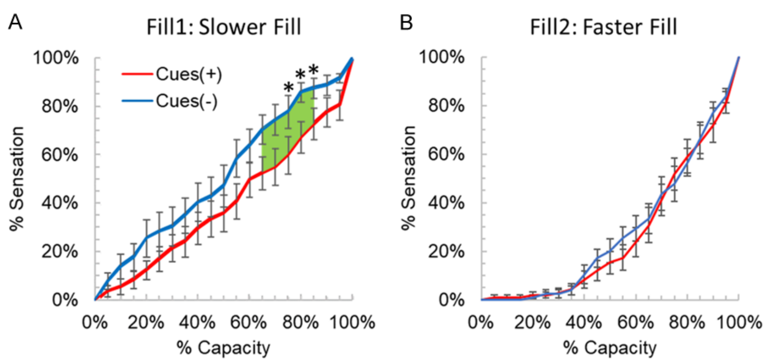

Figure 4. Comparison of sensation-capacity curves for the Cues(+) versus Cues(-) groups for the slower Fill1 (A) and the faster Fill2 (B). In the slower Fill1 (A), the Cues(+) group showed decreased sensation (right shift) compared to the Cues(-) group based on categorical analysis of area under the curve (AUC) from 65% to 85% capacity (green shaded area, Fisher's exact test, P=0.039) and based on AUC from 75% to 85% capacity analyzed as a continuous variable (*, t-test, P=0.047). In the faster Fill2 (B), the Cues(+) and Cues(-) curves were not different throughout filling (t-tests, P>0.05).

some patients [21], and Victor et al. recommended using extinction protocols for individuals with OAB where presentation of a conditioned stimulus, for example the front door in latchkey incontinence, is presented without allowing it to be paired with the unconditioned stimulus (voiding) [20]. Locke et al. recently completed a magnetic resonance imaging (MRI) study in individuals with urge urinary incontinence and identified increased activity in the prefrontal cortex and increased sensations of urgency in response to subject-specific cue images [36]. Furthermore, Macnab et al. used brain functional near infrared spectroscopy (fNIRS) to measure cortical activity during bladder filling [37]. They found increased oxyhemoglobin during filling and an abrupt decrease in oxyhemoglobin in response to an unexpected distractor stimulus [37]. Together, these studies motivate further investigation of potential brain-mediated mechanisms affecting bladder sensation and urgency.

The "cues" effect in the current investigation was only seen during the initial (slow) fill and not observed during the second (fast) fill. This is important because slow filling is more likely to represent normal, everyday bladder function. The lack of observed differences due to A/V cues for faster filling in Fill2, is consistent with previous studies showing that the effect of fill rate has the greatest impact on bladder sensation [14, 38, 39]. This was specifically demonstrated in a previous investigation where external bladder compression affected sensation during slow, but not fast filling [14]. Robertson et al. found an association between faster filling and greater voided volumes in healthy subjects [38], and Thuroff et al. found that the desire to void occurred at smaller volumes during natural filling compared to faster filling with cystometry in healthy men [39]. Furthermore, preclinical studies have demonstrated that fast filling may desensitize afferent mechanosensitive nerves [40, 41] and support our own finding of a lack of sensation differences for the faster filling in Fill2. In addition, this study used data from the second visit to avoid any affects from Sensation Meter training [14].

There is a growing recognition that invasive urodynamics may not be appropriate for the evaluation of bladder sensation [16, 17, 42, 43]. This has prompted our group [10, 13, 14] and others [9, 44, 45] to develop non-invasive oral hydration protocols. These studies have the advantage of physiologic fill rates and could potentially be performed at home with virtual monitoring.

The present study was limited by the use of healthy volunteers without inclusion of individuals with OAB. However, this allowed elimination of extraneous variables that may have influenced bladder sensation. In addition, participants were not randomized to blinding or unblinding as the study was performed sequentially. However, the data helped to identify clear A/V cues that can influence bladder sensation. Future investigations will be required to determine the influence of A/V cues in individuals with OAB.

Conclusion

This investigation demonstrated the influence of A/V cues on patient-perceived sensation of bladder filling during an oral hydration protocol. Our results showed that healthy volunteers with normal bladder function who were shown 3D ultrasound bladder images and were able to hear their bladder volumes during filling had a decrease in sensation. Future studies will be required to determine if A/V cues can be used as potential therapy for OAB.

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Disclosure of conflict of interest

None.

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