314 - OAB supraspinal control network: an ALE meta-analysis and a resting-state functional connectivity review

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HYPOTHESIS AND AIM

In light of a better understanding of supraspinal control of non-neurogenic overactive bladder (OAB), the prevalence of which increases with age, functional imaging has gained significant momentum. The objective of this study was to perform first a systematic review and a coordinate-based activation likelihood estimation (ALE) meta-analysis of all neuroimaging evidence on supraspinal OAB control in response to bladder filling and to report novelties concerning resting state functional connectivity.

STUDY DESIGN AND METHODS

A systematic search of all relevant publications was conducted in PubMed and EMBASE from 1990 till November 2021. Pubmed search, abstract and full text selection was aided by Silvi® (Silvi.AI, Copenhagen, Denmark), an online artificial intelligence aided meta-analysis platform. For the first part of the review, a set of keywords were used including “overactive bladder” or “detrusor hyperactivity” or “urgency urinary incontinence” combined with “neuroimaging” or “PET” or “SPECT” or “supraspinal control network” or “fMRI” and “resting-state functional connectivity” (rs-fcMRI) in order to identify relevant fMRI, PET or SPECT and rs-fcMRI studies on brain activation in non-neurogenic OAB adult patients aged 18 years or older. Concerning the ALE meta-analysis, inclusion criteria resumed to studies that used whole-brain and reported region of interest (ROI) coordinates using Montreal Neurological Institute (MNI) or Tailarach referencing system focusing only on non-neurogenic OAB adult patients aged 18 years of older differentiating between full bladder, high bladder filling, urine withholding or urgency and an empty bladder. Exclusion criteria were (a) studies reporting only rest-state neuroimaging results, (b) studies only reporting functional connectivity, (c) studies only employing predefined ROIs analysis, (d) studies providing only between-group comparisons. ALE analysis uses all the reported foci from the included studies as a spatial probability distribution centered at the given coordinates. The analysis accommodates the spatial uncertainty of neuroimaging findings and uses a spatial variance model. A fixed threshold was used for the ALE map at cluster-level inference threshold with an uncorrected cluster forming threshold of p <0.001 and voxels <100 mm3. Results were presented on a Tailarach template available on BrainMap (https://brainmap.org/ale) using Mango version 4.1.1531 (Research Imaging Institute, https://ric.uthscsa.edu/mango/), a multi-image viewing software

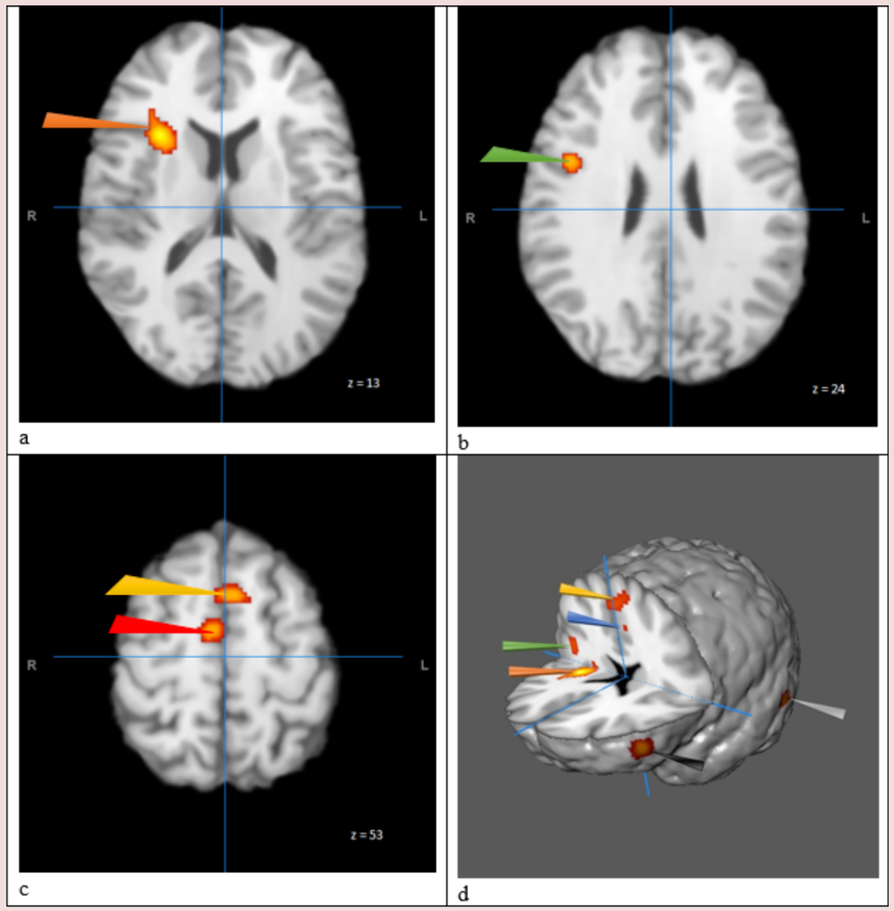
RESULTS

In total and for the first part of the systematic review, 241 non-duplicate citations were screened. 22 full articles were retrieved and 10 were retained after the first selection process. A summary is displayed in table 1. For the ALE meta-analysis, coordinates were extracted from 5 experiments involving 70 patients including 19 men and encompassing 43 foci. ALE meta-analysis showed activation of the insula, supplementary motor area (SMA), dorsolateral prefrontal cortex (PFC), anterior cingulate gyrus (ACG), and temporal gyrus using a threshold of uncorrected p<0.001. A 3D graphical representation is presented in figure 1. 5 articles included a rs-fcMRI

RESULTS

Author, year	Number of participants	Age, M:F	intervention	Imaging modality, analysis software	Imaging paradigm, bladder filling technique
Yin, 2008	19 patients with DO 8 healthy controls	68.3 (48-77) 19:0	-	SPECT NEUROSTAT	Strong desire to void\urgency vs empty bladder Natural + furosemide injection
Griffiths, 2008	11 females with UUI 10 female controls	Median UUI: 56.5 Median HC: 71 (26-85) 0:21	-	fMRI – 3T SPM2	Strong desire to void vs bladder at 100 ml Catheter filling
Tadic, 2008				Secondary analysis exploring network connectivity.	
Tadic, 2012	30 OAB patients > 60 years old subgroup analysis: 9 DO vs 21 non-DO	DO: 76.9±6.4 Non-DO: 70.2±7.3 0: 30	4 patients on medication	fMRI-3T SPM5	Strong desire to void\urgency vs empty bladder Catheter filling
Walter, 2021	12 OAB patients 12 HC	OAB: 40 (32-42) HC: 34 (28-44) 0:24	-	fMRI-3T SPM12	High task (full vs empty) Catheter filling
RESTING-STATE FUNCTIONAL CONNECTIVITY					
Nardos, 2016	16 patients with UUI 24 healthy controls	UUI: 55.8± 7.6 HC: 59.8 ±13.3 0:40	-	fMRI-3T **rs-fcMRI** in-house software-build with IDL	Strong desire to void\urgency vs empty bladder Catheter filling
Ketai, 2016	53 OAB patients 20 female controls	OAB: 53.2±5.8 HC: 55.2±10.8 0:73	-	fMRI-3T **rs-fcMRI**	Hold vs withdrawal vs full bladder Catheter filling
Zuo, 2019	26 OAB patients 28 Healthy controls	OAB: 43.6 ±13.4 HC: 50.1±12.1 5:49	-	**Rs-fcMRI**-3T DPABI	-
Zuo, 2019				**Rs-fcMRI**-3T DPABI	-
Ketai, 2021	30 OAB patients + hypnotherapy 34 OAB patients + pharmacotherapy	Hypnotherapy: 54±13 Pharmacotherapy: 57±10 0:64	Hypnotherapy Pharmacotherapy (oxybutinine or tolterodine)	fMRI-3T **rs-fcMRI**	High volume filled vs empty bladder Catheter filling

Characteristics of studies retained after full-text review. OAB = overactive bladder, M= males, F= females, fMRI = functional magnetic resonance imaging, rs-fcMRI=resting state functional connectivity magnetic resonance imaging, HC = Healthy controls, UUI = urgency urinary incontinence, SPECT = single-photon emission computed tomography, SPM = Statistical Parametrical Mapping, DPABI = data processing and analysis of brain imaging software,, and T = Tesla.



Areas of the brain activated during bladder filling: results of the meta-analysis using brain coordinates of subjects from 4 studies (5 experiments) with 43 relevant foci among 70 patients. (a) axial cut at z = 13, (b) axial cut at z = 24, (c) axial cut at z = 53, (d) 3D representation. Orange arrow: right anterior insula, green arrow: right dorsolateral prefrontal cortex, red arrow: right supplementary motor area, yellow arrow: left supplementary motor area, blue arrow: left anterior cingulate gyrus, , white arrow: left middle/inferior temporal gyri, black arrow: left dorsolateral prefrontal cortex

INTERPRETATION

This study is the first to report an ALE meta-analysis specific to bladder filling in patients with non-neurogenic OAB. The right insula seems to be a mutual activation region in healthy subjects and non-neurogenic OAB patients with activation increasing by bladder filling. The dorsolateral PFC was also demonstrated and possibly exerts an inhibitory effect of the voiding reflex by direct effect on the PAG in order to maintain continence. The ACG, thought to monitor autonomic, emotional and motor arousal and, in response to bladder filling in healthy adults, seems to be implicated in the subjective awareness of bladder fullness and the desire to void and was also shown to be in a recent ALE meta-analysis as a center of control of pelvic floor muscle contraction. The temporal lobe was also shown as an activated region among non-neurogenic OAB, a region that is not normally activated during filling among healthy subjects and may be regarded as a part of a compensatory pathway among non-neurogenic OAB patients in the process of suppressing voiding. The SMA, shown as an activated region in our meta-analysis as well, is anatomically adjacent to the dorsal ACC and both are usually co-activated. The SMA was also identified by a previous ALE meta-analysis as a pelvic floor muscle contraction center and participates in a back-up mechanism to maintain continence.
Five studies implementing rs-fcMRI were included in this review. Supraspinal centers identified in our ALE meta-analysis are based on studies with results on observations of activity in specific brain regions following a specific task, such as high bladder filling or urine withholding, and thus imply correlation but not causality between supraspinal centers and OAB. A recent fMRI technique, with a stronger statistical inference, rs-fcMRI, evaluates spontaneous low-frequency signal fluctuations between distant but functionally related brain regions in the absence of a specific task and contributes to the elaboration of specific regions called resting-state networks (RSN) with potential functional relevance. Atypical activation of various RSNs was demonstrated, first the interoceptive network, consisting of the ACC and the insula, the ventral attention network, consisting of the temporoparietal junction and ventral PFC activated in response to unexpected behavioral stimuli, the sensorimotor related network, and the default mode network consisting of the medial PFC and posterior cingulate cortex. Rs-fcMRI showed, with greater statistical inference than fMRI, the involvement of a supraspinal component in bladder overactivity, which may be responsible for its genesis or a consequence of failed or successful adaptation. It is a powerful tool to phenotype OAB and to constitute a substrate for behavioral treatments among other, hypnotherapy.

CONCLUSION

Five common areas activated among non-neurogenic OAB patients were identified and RSNs exhibited atypical functional connectivity. Hence, the OAB bladder-brain control network (BBCN) could be conceived as a dynamic homeostatic system, influenced by several structural and functional inputs with the aim of symptomatic control and maintenance of continence. Recruitment of accessory pathways outside of the classically described BBCN such as the temporal lobe and the cerebellum, in order to maintain continence and social property by triggering pelvic floor muscle contraction and inhibiting pontine centers of micturition, is a neuroplasticity feature seen in OAB patients. A clear intrinsic supraspinal physio-pathological component is not yet clearly elucidated, however with the armamentarium of functional imaging, and most recently the rs-fcMRI analysis, an OAB neuro-signature, can help allocate patients to a successful treatment as opposed to a therapeutic approach based on invasiveness escalation.