Brain Mechanisms Underlying Urge Incontinence and its Response to Pelvic Floor Muscle Training

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Abbreviations and Acronyms

dACC = dorsal anterior cingulate cortex

DO = detrusor overactivity

fMRI = functional MRI

LUT = lower urinary tract

MMSE = Mini Mental State Examination

mPFC = medial prefrontal cortex

MRI = magnetic resonance imaging

PAG = periaqueductal gray

PFMT = biofeedback assisted pelvic floor muscle training

ROI = region of interest

SMA = supplementary motor area

UUI = urge urinary incontinence

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Purpose: Urge urinary incontinence is a major problem, especially in the elderly, and to our knowledge the underlying mechanisms of disease and therapy are unknown. We used biofeedback assisted pelvic floor muscle training and functional brain imaging (functional magnetic resonance imaging) to investigate cerebral mechanisms, aiming to improve the understanding of brain-bladder control and therapy.

Materials and Methods: Before receiving biofeedback assisted pelvic floor muscle training functionally intact, older community dwelling women with urge urinary incontinence as well as normal controls underwent comprehensive clinical and bladder diary evaluation, urodynamic testing and brain functional magnetic resonance imaging. Evaluation was repeated after pelvic floor muscle training in those with urge urinary incontinence. Functional magnetic resonance imaging was done to determine the brain reaction to rapid bladder filling with urgency.

Results: Of 65 subjects with urge urinary incontinence 28 responded to biofeedback assisted pelvic floor muscle training with 50% or greater improvement of urge urinary incontinence frequency on diary. However, responders and nonresponders displayed 2 patterns of brain reaction. In pattern 1 in responders before pelvic floor muscle training the dorsal anterior cingulate cortex and the adjacent supplementary motor area were activated as well as the insula. After the training dorsal anterior cingulate cortex/supplementary motor area activation diminished and there was a trend toward medial prefrontal cortex deactivation. In pattern 2 in nonresponders before pelvic floor muscle training the medial prefrontal cortex was deactivated, which changed little after the training.

Conclusions: In older women with urge urinary incontinence there appears to be 2 patterns of brain reaction to bladder filling and they seem to predict the response and nonresponse to biofeedback assisted pelvic floor muscle training. Moreover, decreased cingulate activation appears to be a consequence of the improvement in urge urinary incontinence induced by training while prefrontal deactivation may be a mechanism contributing to the success of training. In nonresponders the latter mechanism is unavailable, which may explain why another form of therapy is required.

Key Words: urinary bladder, overactive; brain; urinary incontinence, urge; magnetic resonance imaging; biofeedback, psychology

PREVALENT, morbid and costly, UUI is a major problem for older adults. Although generally attributed to DO, its actual causes remain uncertain.[1,2] Despite many treatment advances in the last 50 years mechanisms of disease and therapy (behavioral or pharmacological) remain unclear and

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available treatments are still not curative. Therefore, we determined factors that predict or mediate the response to behavioral treatment, reasoning that predictors should help identify possible UUI phenotypes with different responses to treatment while mediators of improvement might reveal the mechanism of therapy.[3] We expected that this new knowledge would help enhance treatment efficacy.

In a previous study of PFMT,[3] which is a widely recommended behavioral treatment for UUI,[4,5] we found that urodynamic parameters neither predicted nor mediated the response to treatment. The only exception was the strength and velocity of DO, which predicted a poor response but only in subjects with elicitable DO. Having excluded most peripheral (urodynamic) aspects as convincing predictors or mediators, in the current study we focused on central (brain) control of the LUT.

The LUT normally alternates between periods of urine storage and shorter periods of voiding.[1,6] During storage as the bladder fills, bladder sensation normally increases from none through first desire to void to strong desire to void[7] until it is interrupted by voluntary voiding. In UUI brain control is abnormal, that is sensation is altered and voiding may occur involuntarily.

According to a provisional model of brain-bladder control developed in the last decade 3 neural circuits help maintain continence by suppressing the spinobulbospinal voiding reflex at its terminus in the PAG (fig. 1).[1,2,6,8,9] Circuit 1 involves the mPFC, and its afferent and efferent pathways, possibly including the insula, while circuit 2 involves the dACC (midcingulate) and the adjacent SMA, and circuit 3 may involve subcortical regions such as the parahippocampal complex.[10]

In strictly normal subjects such as the controls in this study circuits 1 and 2 are not significantly activated during storage but circuit 1 (mPFC) is activated during voluntary voiding.[11,12] In UUI subjects we expected that there would be abnormalities in brain activation provoked by bladder

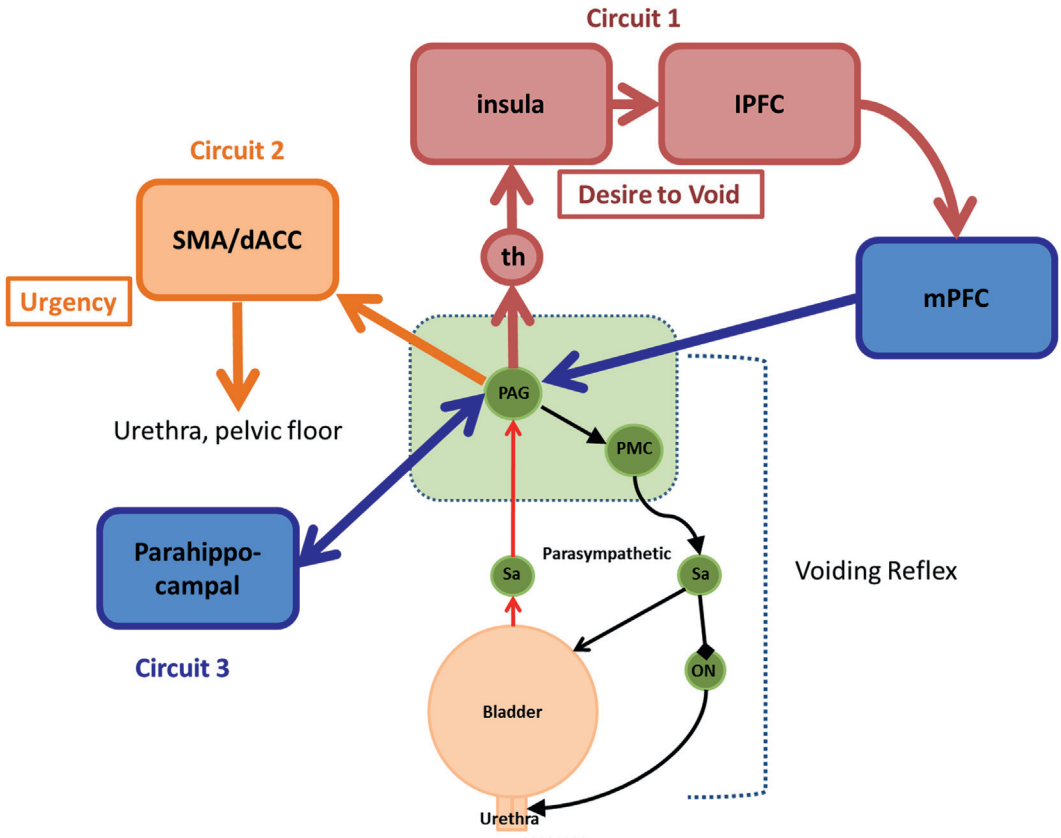

Figure 1. Simplified working model of brain/bladder control system. Voiding reflex incorporates PAG and pontine micturition center (*PMC*) in brain stem (green areas), which control contraction and relaxation of bladder and urethral muscles via sacral parasympathetic regions (*Sa*) and Onuf nucleus (*ON*). This reflex is controlled by 3 cerebral neural circuits. Circuit 1 involves thalamus (*th*), insula and lateral prefrontal cortex (*lPFC*) with mPFC regulating executive control of voiding. Circuit 2 involves dACC and SMA, which together generate urgency sensation and provide motor output to pelvic floor/sphincter mechanism. Parahippocampal complex is part of putative subcortical circuit 3. Red and yellow areas indicate regions typically activated by bladder filling. Blue areas indicate regions deactivated by bladder filling. Adapted from de Groat et al.[1]