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DIFFERENCES IN THE FUNCTION OF THE PREFRONTAL CORTEX BETWEEN WOMEN WITH URGE URINARY INCONTINENCE AND CONTINENT COHORTS

Hypothesis / aims of study: **Aim 1.)** To determine if women with symptoms of urge urinary incontinence (UUI) have changes in the prefrontal cortex (PFC) that affect their ability to effectively control information processing and produce circumstances that impair performance on voluntary behavioral tasks, it was **hypothesized** that women with good control of bladder function (continent) **1.)** Would perform better than cohorts with UUI in the processing of information that interferes with the retention of a behavioral goal in working memory (WM), **2)** Would perform better than cohorts with UUI in the ability to hold a single crucial goal in WM and suppress a reflexive response to a stimulus, and **3)** Would perform better than cohorts with UUI on the ability to flexibly alternate between stimuli and shift behavioral goals in response to changing circumstances**. Aim 2.)** To determine if women with UUI have changes in the lower urinary tract (LUT) that decrease their ability to perceive sensations of bladder filling and reduce storage capacity of the bladder, it was **hypothesized** that **1.)** Continent women would perform better than cohorts with UUI on the ability to perceive a first desire to void (FDV) and experience a strong desire to void (SDV) at higher urine volumes, and **2)** Women who performed well on behavioral tasks used to measure cognitive processes in the PFC would be able to perceive both a FDV and SDV, perceive these sensations at higher urine volumes, and when a SDV was perceived would be able to delay micturition for two minutes.

Study design, materials and methods: Design: Since a behavioral study of prefrontal brain function and bladder sensory perception of people with symptoms of UUI has never been undertaken, this study was designed as an exploratory between group design. **Methods:** Twenty women expressing symptoms of UUI and twenty continent women 60 to 79 years of age and living in the community were recruited to comprise the independent samples. **Inclusion Criteria:** 1) Women 60 to 79 years of age, 2) Expressing symptoms of frequency, urgency, a sudden strong desire to void accompanied by incontinence but without evidence of urine leakage with coughing or a post void residual > 100cc's after urinating (Group 1) or (Group 2) no involuntary urine loss for 1 year, 3) Can hold urine for one hour without a need to void, 4) Have a 9th grade education level or higher with the ability to read, write and speak English, 5) Are right handed, 6) Can read newspaper print (both eyes, with correction), 7) Can hear normal conversation, and 8) Demonstrate a Mini-Mental Status Examination (MMSE) score of 25 or greater (a high probability of intact cognition). **Exclusion criteria:** 1) A history of stroke, cerebral hemorrhage, Parkinson's disease, head injury, seizure disorder, transient ischemic attacks, spinal stenosis or injury, cognitive impairment, congestive heart failure, diabetes mellitus, hypercalcemia, untreated B12 or thyroid deficiency, or alcoholism, 2) A history of bipolar depression, schizophrenia, or psychosis, 3) A history of brain or spinal cord surgery, radical pelvic surgery, chemotherapy or radiation therapy to the pelvic area, or surgery for urinary incontinence, 4) Use of tranquilizers, hypnotics, prescription analgesics, antihistamines, antipsychotics, antiseizure medication, anticholinergics, and alpha agonists and antagonists, 5) A history of involuntary urine loss without warning, 6) Pedal edema of the lower extremities, 7) An inability or unwillingness to stop medication for urinary incontinence 2 weeks prior to cognitive testing, or 8.) Evidence from urinalysis of a urinary tract infection, hematuria, and/or glycosuria. **Procedures (after telephone screening for inclusion and exclusion criteria):** During **the first visit (2 hours)**, all volunteers completed a screening urinalysis, the MMSE, a test of ability to read newspaper print and listen and respond to normal conversation, and assessment for pedal edema. Volunteers with UUI were screened for stress and overflow incontinence: 1.) The bladder was scanned to determine that 250cc's of urine was present, 2.) Volunteers stood and coughed hard three times with a brown paper towel between their legs to detect urine leakage, and 3.) After voiding, the bladder was scanned again to determine the amount of residual urine. Leakage immediately after coughing or more than 100cc's of residual urine in the bladder resulted in exclusion of UUI volunteers from the study. All participants were asked to drink water until they first noticed a need to urinate at the next earliest convenient opportunity, first desire to void (FDV). During bladder filling, the Weschler-III-Abbreviated (WMS-III-A) evaluation for immediate auditory and visual memory was administered. Participants were asked to complete a demographic questionnaire, and subjects with UUI were asked to complete an Incontinence Symptom Index as well. Thirty-five minutes later, all participants completed the delayed portion of the WMS-III-A. When a FDV was expressed, participants were asked to indicate the strength of the need to void by placing an X along a continuum from 0 to 10 on a Bladder Sensation Intensity Scale. A bladder ultrasound was performed to measure urine volume at this sensory point. When a strong desire to void (SDV, the need to void immediately) was expressed, participants again filled out the Bladder Sensation Intensity Scale and then were asked to delay voiding for 2 minutes before expelling urine into a measuring receptacle. The ability to delay voiding was timed from the point at which the request to void was made until 2 minutes had passed or voiding occurred (whichever occurred first). After completing assessment of the lower urinary tract, participants were scheduled for their second visit. During the **second visit (1 hour),** the following cognitive measures of PFC function were administered: 1.) Operation-Word Span (OSPAN), 2.) Stroop Test, 3.) Trail-Making Test A and B (TMT A and B), and 4.) The Wisconsin Card Sorting Test (WCST). After these cognitive tests were administered, the subject's participation in the study was complete.

Results: In this study, 75% of women with UUI rated bother and severity of their incontinence as low. Using Mann-Whitney U because of sample size and non-normality of the sample distribution, incontinent women were revealed to be significantly slower than continent cohorts on speed of cognitive processing (Stroop Dot task, n = 20/ group, p = .044) and approached significance as being unable to keep track of the card-sorting category of the moment (WCST, n = 20/group; p = .057). Working memory capacity (WMC), the ability to control information processing, was derived by dividing each group of subjects into upper (high-span) and lower halves (low-span) by the number of words recalled correctly on OSPAN. Low-span incontinent and continent women were not significantly different, but high-span

incontinent (n = 10) women had a significantly lower number of words recalled ($\overline{X}$ = 16.6 + 3) than high-span continent (n = 9) cohorts ($\overline{X}$ = 21.6 + 5.2; U = 21.5; p = .053). There were no significant differences between groups for a FDV or a SDV, for urine volume at a FDV or SDV, or for ability to delay micturition for 2 minutes at a SDV. The following findings are from the upper and lower quartiles of the sample distribution for WMC: 1.) High-span continent subjects approached significance as having a higher bladder volume at a FDV than high-span incontinent cohorts (p = .076), 2.) High-span incontinent women compared to low-span incontinent women had a significantly higher bladder volume at a SDV (p = .009), and 3.) High-span continent women compared to low-span continent women had significantly higher bladder volumes at a FDV (p = .028) and at a SDV (p = .009). **Power:** Design: Independent samples: alpha=0.05, power=0.8, DIFF=5, SIGMA=3.6 (pooled), M=1.1, Sample size = 9/group.

Interpretation of results: One of the most significant findings was that incontinent women demonstrated poorer working memory capacity (WMC) than continent cohorts. WMC is "about using attention to maintain or suppress information" p. 20 **(1)** and is the product of neural processes in the prefrontal cortex (PFC) that are fundamental constituents of cognitive functions that influence behavioral performance **(2, 3)**.

Concluding message: The primary purpose of this study was to determine if women with good control of bladder function (continent) would perform better than women expressing symptoms of urge urinary incontinence (UUI) on behavioral tasks that depend on cognitive processes in the prefrontal cortex (PFC). The behavioral tasks selected to measure these cognitive processes require the ability to control behavior and direct it toward a selected goal similar to the voluntary control of bladder function during the delay between the perception of bladder fullness and the decision to urinate. WMC, as a latent variable, appears to be the "common factor" affecting behavioral performance and as a predictive variable, is able to predict behavioral performance on a variety of cognitive tasks. UUI is multifactorial, but lesion and neuroimaging studies suggest that a "brain factor" may be contributing to this disorder.

References: **(1)** Current Directions in Psychological Science (2002) 11: 19-23, **(2)** Psychonomic Bulletin and Review (2002) 9: 637-671, and **(3)** Neuroscience (2006)139: 23-38.

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HUMAN SUBJECTS: This study was approved by the Institutional Review Board: Medicine and followed the Declaration of Helsinki Informed consent was obtained from the patients.