A Cortico-Neurocentric Approach to LUTS
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Vesicocentric thinking
- Bladder thought to be autonomous or reflexive
- Bladder size is too small
- Isolated de novo detrusor problems
- UTI's due to bladder lining problems or poor hygiene
- Bowel pushes up against the bladder and decreases capacity
- Accidents are due to immaturity of the brain

Evolution to a Cortico-Neurocentric Theory
- Anticholinergics didn’t work for everyone
  - Some kids got better for a brief period and then became worse
  - Some kids never had any response
  - Children with ADD/ADHD had little or no response to Anticholinergics
- Biofeedback didn’t work for all and did little for urgency problems

Evolution to a Cortico-Neurocentric Theory: Our experience
- Pts with bulbar urethritis that had OAB responded to hytrin
- We began using hytrin to treat OAB
- Tegaserod was used for constipation and the patients responded with an improvement in constipation but also an elimination of pvr
- Pts who responded to Botox A injections for ESD did not have elimination of OAB symptoms with specific treatment

Evolution to a Neurocentric Theory: Our experience
- Many patients would respond with elimination of the OAB symptoms when treated for underlying Neuropsychiatric problems
- Patients who had NE refractory to DDAVP that were treated with Imipramine responded with an improvement in diurnal OAB symptoms.

Evolution to a Cortico-Neurocentric Theory: Bowel Bladder Interaction
- Bowel regimens that softened stool only, did not work as well as those that utilized cathartics
- We noticed persistent external sphincter dyssynergia on EMG during biofeedback in constipated children
- Most kids have a tendency to relapse within 6-12 mo
- Children seem to wet more after lunch and dinner
Bowel - Bladder interactions

- This helps substantiates the idea that there could be a persistent problem with peristalsis in the gut
- This problem could possibly be due to deficient 5HT levels
  - Zelnorm Study

Colonic contractions and OAB

- Warne et al found on a 24 hr continuous urodynamic studies that colonic contractions were found to precede bladder contractions

Bowel Bladder and Cortico-Neurocentric Interaction

- Jia et al showed that there is a defect in the Parasympathetic Nucleus (PSN) in patients with Imperforate Anus
- PSN is also involved in micturition modulation
- PSN innervated by $\alpha$-Adrenergic pathways descending from the Locus Coerulus
- PSN sends excitatory fibers to the Preganglionic Neurons

Colitis and OAB

- We noted that patients with colitis had a tendency to have OAB and their symptoms would improve as soon as the colitis was improved.
- Pezzone et al. reported that acute colitis triggers bladder hyperactivity in rats, providing experimental evidence for crosstalk between different pelvic viscera.

Evolution to a Cortico-Neurocentric Theory: Bowel Bladder Interaction

- Rectal diameter > 4 cm on US was associated with dysfunctional voiding
- In a study by Miyacato et al, the researchers found that rectal distention leads to decreased amplitude and shortened duration of bladder contraction and finally can almost abolish bladder activity.

Chemical "cross-talk" between pelvic viscera may influence a number of functional pain syndromes
The Brain and Micturition Control

- Why would children have developmental delays in micturition control without exhibiting other motor developmental problems?
- On the other hand why do pts with learning disabilities and neuropsych problems with no motor problems exhibit voiding problems?

Brain centers of Micturition

- To define forebrain structures involved in volitional bladder control, traditional clinical-neuropathological studies have relied upon the association between acquired brain lesions and the development of urinary incontinence.
- Nearly 75% of stroke patients with frontal lobe lesions developed urinary incontinence (Sakakibara et al 1999).
- Right superior frontal damage has been linked with transient urinary incontinence while bilateral damage has been associated with permanent incontinence (Mochizuki & Saito 1990).
- These studies suggest that the frontal lobes in general, and the superior frontal gyrri in particular, are important in volitional bladder control.

Brain centers of Micturition

- In normal controls,
  - the left superior frontal gyrus,
  - supplementary motor area,
  - cingulate gyrus,
  - left orbitofrontal cortex,
  - bilateral frontal opercula and insula
  - were activated during a strong urge to void, using an fMRI paradigm
- (Kuhtz-Buschbeck et al 2005)

Brain centers of Micturition

- PET studies have implicated the
  - mid-cingulate and prefrontal cortices bilaterally
  - right inferior frontal gyrus
  - parts of the premotor cortex
  - cingulate gyrri bilaterally, right anterior cingulate gyrus,
  - left superior prefrontal, middle frontal, and anterior cingulate gyrri, and left insular cortex
  - in the neural regulation of volitional bladder control

Urge-incontinent adults

A specific condition as probe of bladder control

Urge incontinence adults experience:
1. abnormal sensation
   - "urgency"
   - strong motivation to void
   - fear of embarrassment
   - a social emotion
2. abnormal brain responses to bladder filling
   - even when no bladder spasm (DO) to actual incontinence

Clues from cardiac physiology

Socially stressful task (speech preparation) deactivates vmPFC and activates dACC
- 2 mechanisms to increase heart rate

Socially stressful situation (urgency) deactivates vmPFC and activates dACC
- 2 mechanisms to suppress voiding
**Brain centers of Micturition**

- Insula
  - Mapping Visceral Sensation
  - Encodes sensory feedback from the bladder that enables the brain to exert effective control
  - Normal patient reported sensations of bladder filling and desire to void

- ACG
  - Autonomic, emotional control and motor control and in monitoring
  - The anterior gyrus is associated with executive activity

**Brain centers of Micturition**

- PMC
  - Specific to motor control of the lower urinary tract

**Brain and Bladder Activity during fMRI**

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Normal Low bladder vol</th>
<th>Normal High bladder vol</th>
<th>Urge Low bladder vol</th>
<th>Urge High bladder vol</th>
<th>Incontinent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insula</td>
<td>Rt side low</td>
<td>Rt side high</td>
<td>Weaker than N’s</td>
<td>Stronger than N’s</td>
<td></td>
</tr>
<tr>
<td>ACG</td>
<td>Weak</td>
<td>Weak</td>
<td>Strong</td>
<td>Stronger as void gives up</td>
<td>Weak or absent</td>
</tr>
<tr>
<td>PAG</td>
<td>Trend towards activation</td>
<td>Low level of Activity</td>
<td>Activation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMC</td>
<td>Elevated</td>
<td>Stronger</td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Urgency**

- Urgency
  - is a social emotion
  - strong motivation to void
  - fear of embarrassment
  - activates dACC
  - sympathetic motor cortex
  - and deactivates vmPFC
  - parasympathetic motor cortex
  - to suppress voiding reflex
  - ACG appears to have an inhibitory effect on the PMC via indirect pathways since there is no monosynaptic connection to the PMC

**Normal adults: responses to filling at small bladder volume, weak filling sensation**

- insula
- dorsal anterior cingulate (dACC, very weak)
- dorsolateral prefrontal (dIPFC, weak)
- and other regions
Normal adults: responses to filling at large bladder volume, strong desire to void

- **Activated:**
  - insula: more strongly
  - dACC: still weak
- **Deactivated:**
  - medial PFC: weak but consistent

Responses to bladder infusion in normal controls at large bladder volumes

- Insular response is greater on the right.
- RI = right insula; ACG = anterior cingulate gyrus; H = hypothalamus; RI/PFC = right anterior insula and/or lateral prefrontal cortex. R = right side. Color bar shows scale of student's t values. Griffiths et al. Page 11 Neuroimage.

Responses to bladder infusion in subjects with urge incontinence at large bladder volumes.

RI = right insula; ACG = anterior cingulate gyrus; PMC = pontine micturition center.

Comparison of normal vs. pts with urge

Selective Sacral Stimulation and the AC and PC Gyri

- Dasgupta et al. Have shown that there are significant changes in the cingulate gyrus (AC) when spinal stimulation is activated.
- It is reciprocally connected to other cortical and brain stem centers including the amygdala, the hypothalamus, the PAG, the substantia nigra and the ventral tegmental area.

**Why do kids wet without knowing?**

- There is weak or incomplete inactivation of the anterior cingulate gyrus which is essential to inhibit the PMC via indirect pathways.

**Perception of Pain**

- Painful stimuli are picked up and processed in the insula and ACG.
- There are numerous interconnections to the “Flight or Flight” regions of the midbrain PAC.
- There is partial segregation of function between pain, affect and sensation.
- The ACG may reflect our emotional experience that provokes our reactions to pain.

**What is the Role of Behavior and OAB**

- We looked at our series of 300 patients with Urgency/Frequency and found that refractory patients had a common link: 50% had a neuropsychiatric problem within the Syndrome Mix or had a close family member with it.

**Psychiatric problems and OAB**

- Large population studies found:
  - Children who have problems with incontinence, the incidence of behavioral and psychiatric disorders is three times greater than in the general population.

**Enuresis and Neuropsychiatric Problems**

- Two studies found increased rates of childhood enuresis in children with ADHD (28–32%) (Biederman et al 1995; Neveus et al 2000);
- One study found increased rates of enuresis in childhood Tourette’s syndrome (22%) (Comings & Comings 1987).

**Enuresis and Neuropsychiatric Problems**

- Secondary enuresis, but not primary enuresis, was associated with an increased rate of behavioral problems (Feeney et al 1990).
- In Chinese children, persistent enuresis after 4 years of age is associated with increased behavior problems, as reported by both parents and teachers (Liu et al 2000).
- A similar finding was reported in US children with enuresis persisting after 5 years of age (Byrd et al 1996).
Enuresis and Neuropsychiatric Problems

- Kraeplin 1919: "obstinate nocturnal enuresis" in cases of dementia praecox.
- Crow et al 1995: pre-schizophrenics were said to be more likely enuretic by day at age 3 and at night by age 5 than controls.
- Jones 1997: analyzing the same cohort concluded that at age 7 individuals who subsequently went on to develop schizophrenia were more likely to have incontinence than normal controls.

A study of child/adolescent-onset schizophrenia found late onset of obstinate nocturnal enuresis (enuresis in adult bipolar disorder (18%)). Persistent enuresis has also been associated with an increased risk of adolescent suicidal behavior (Liu & Sun 2005). Persistent enuresis after the age of 10 years has been associated with a small but significantly increased risk of conduct problems, attention deficit behaviors, and anxiety/withdrawal in adolescence (Fergusson & Horwood 1994).

Enuresis as a Premorbid Developmental Marker of Schizophrenia

- Hyde et al hypothesized that if the abnormalities in SCZ are related to frontal lobe development, then since maturation and functional competence of the frontal lobes also are important in the acquisition of volitional bladder control in children, SCZ patients would have a higher rate of childhood enuresis as a secondary manifestation of their frontal lobe developmental abnormalities.

Enuresis as a Premorbid Developmental Marker of Schizophrenia

- Hyde et al 2007 found increased rates of enuresis in adult bipolar disorder (18%). Persistent enuresis has also been associated with an increased risk of adolescent suicidal behavior (Liu & Sun 2005). Persistent enuresis after the age of 10 years has been associated with a small but significantly increased risk of conduct problems, attention deficit behaviors, and anxiety/withdrawal in adolescence (Fergusson & Horwood 1994).

- 211 patients with schizophrenia (herein "probands" or SCZ) (82.5% male), 234 of their non-psychiatric siblings (43.2% male), and 355 non-psychiatric controls (39.2% male) were included.
- Children were classified as probands if they had any conduct problems, attention deficit behaviors, and anxiety/withdrawal in adolescence (Fergusson & Horwood 1994).

- Children with schizophrenia had significantly higher rates of enuresis than controls (11.5%, p=0.008).
- Female probands had significantly higher rates of enuresis than their non-psychotic siblings (21.3% vs. 11.2%, p=0.01) and controls (21.3% vs. 7.3%, p<0.001).
- Male probands also had significantly higher rates of enuresis than male siblings (23.2% vs. 10.3%, p=0.001) or male controls (23.2% vs. 11.5%, p=0.008).
- Female probands had significantly higher rates of enuresis than female controls (44% vs. 4.6%, p=0.02) but not female siblings (14% vs. 15%, p=0.77).
- No significant differences in rates of enuresis were found between siblings and controls in the overall sample or male subset, but were found in female siblings vs. female controls (12%) vs. 4.6%, p=0.02).

- 808 pts
- Subjects were between the ages of 18-60. Participants included 211 patients with schizophrenia (herein "probands" or SCZ) (82.5% male), 234 of their non-psychiatric siblings (43.2% male), and 355 non-psychiatric controls (39.2% male).
- A history of enuresis was obtained from the mother of each participant by applying DSM-IV.
- Neurological/medical co-morbidity contributing to childhood enuresis was evaluated through subject and maternal interviews.
- Subject cohorts were subdivided into those with or without a history of childhood enuresis.
Gray Matter Volume Decreases in Controls with Enuresis compared with Controls without Enuresis

This figure depicts the statistical main effects of regional gray matter volume decreases in healthy controls with a history of childhood enuresis versus those without a history. The central figure is a frontal view, and the other figures, from left to right, are the left lateral, left medial, right medial, and right lateral hemispheric surface views. The most significant cluster of reduced gray matter volume in healthy controls with enuresis is in the right superior frontal gyrus, BA 9.

Gray Matter Volume Decreases in Probands with Enuresis Compared to Probands without Enuresis

This figure depicts the statistical main effects of decreased regional gray matter volume comparing probands with a history of childhood enuresis to those without a history. The central figure is the frontal view, and the other figures, from left to right, are the left lateral, left medial, right medial, and right lateral hemispheric surface views. The most significant cluster of decreased gray matter volume in probands with enuresis is in the right superior frontal gyrus, BA 9.

Enuresis as a Premorbid Developmental Marker of Schizophrenia

Bradley Peterson et al. Proceedings of the National Academy of Sciences

- Siblings of probands with enuresis had significantly higher rates of enuresis than siblings of probands without enuresis (19.1% vs. 7.0%, p<0.01).
- Probands with enuresis performed significantly worse than probands without enuresis on two measures, both involving speed-dependent verbal retrieval: Letter Fluency and Category Fluency.
- Controls with enuresis performed significantly worse than controls without enuresis on Letter Fluency, and showed a trend towards worse performance on Category Fluency in comparison to controls without enuresis.
- No other significant findings were found between the two control groups on neuropsychological measures.

Enuresis Compared to Probands without Enuresis

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Depression and Cortical Changes

Bradley Peterson et al. Proceedings of the National Academy of Sciences

- Imaging studies of 131 people aged 6 to 54 with and without a family history of depression showed a 28-percent thinning in the right cortex in people who had a family history of depression compared with people who did not.
- They did memory and attention tests on the study subjects and found the less brain material a person had in the right cortex, the worse they performed on attention and memory tests.
- Findings suggest rather strongly that if you have thinning in the right hemisphere of the brain, you may be predisposed to depression and may also have some cognitive and inattention issues.

The Syndrome Mix

- ADD
- ADHD
- Depression
- Anxiety
- Phobia
- OCD
- Oppositional/Defiant behavior
- Asperger’s syndrome
- Tourette’s syndrome
- Bipolar disease
Corticotropic Releasing Factor

- CRF acts in the CNS as a neurotransmitter
- Neurons in the brain project to the Locus Ceruleus (NE) and Dorsal Raphe Nucleus (5-HT)
- Seen in the interomediolateral cell column implicating it in motor control of micturition
- Also found in the dorsal root ganglia and co-localizes with substance p and other peptides

CRF

- Areas critical to the central stress response overlap with control of bladder activity
- CRF levels are elevated in PST and Tourettes, but not in Anxiety, panic or OCD
- After exposure to pain IBS patients experience heightened sensitivity to pain
- CRF antagonists block bladder overactivity in animal models

Learned vs Innate Cortico-neurocentric Problems

- Learned behaviors can lead to bladder problems
- Transient bouts of constipation can lead to voiding problems without having functional transit problems
- 2º bladder changes can occur due to 1º neurocentric problems
- These patients need specific treatment of their bladder changes as well as the 1º central defect

Unified Theory of Voiding Dysfunction

Vesicocentric

Neurocentric