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Sex-related differences in prepulse inhibition of startle in irritable bowel syndrome (IBS)

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ABSTRACT

Alterations in central networks involved in the regulation of arousal, attention, and cognition may be critical for irritable bowel syndrome (IBS) symptom maintenance and exacerbation. Differential sensitivities in these networks may underlie sex differences noted in IBS. The current study examined prepulse inhibition (PPI), a measure of sensorimotor gating, in male and female IBS patients. Relationships between PPI and symptom severity were examined, as well as potential menstrual status effects. Compared to healthy controls, male IBS patients had significantly reduced PPI; whereas female IBS patients (particularly naturally cycling women) had significantly enhanced PPI suggesting hypervigilance. Considering previously demonstrated sex-related differences in perceptual and brain imaging findings in IBS patients, the current findings suggest that different neurobiological mechanisms underlie symptom presentation in male and female IBS patients. Compromised filtering of information in male IBS patients may be due to compromised top down (prefrontal, midcingulate) control mechanisms while increased attention to threat due to increased limbic and paralimbic circuits may be characteristic of female IBS patients.

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1. Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by recurrent abdominal pain or discomfort combined with alterations in bowel function (Longstreth et al., 2006). Increased perceptual responses ("visceral hypersensitivity") to physiologically occurring and to experimentally induced visceral stimuli are a hallmark factor in IBS, and these abnormalities are shared by other functional gastrointestinal (GI) and urological disorders (Azpiroz et al., 2007; Whitehead and Palsson, 1998). While a variety of putative peripheral factors may play a role in visceral hypersensitivity in IBS, there is growing evidence that central mechanisms that enhance responses to interoceptive information ("central pain amplification") are also critical for symptom maintenance and exacerbation (Azpiroz et al., 2007; Mayer, 2000; Mayer et al., 2006). Recent functional brain imaging studies have shown altered responses to the threat of an aversive visceral stimulus in limbic and prefrontal brain regions in IBS, in addition to increased responses to the actual stimulus (Berman et al., 2008). Increased startle responses to threat of aversive visceral and non-visceral stimulation has also been shown in female IBS patients (Naliboff et al., 2008). These studies suggest that IBS patients have enhanced activity in emotional arousal and pain facilitation circuits in the brain related to visceral and non-visceral stimuli. Less is known about the role of specific attentional or information processing deficits that might also play a role in altered IBS responses. We have previously demonstrated that female IBS patients show a failure of habituation of an early evoked potential response, the P50, to auditory stimuli, consistent with altered preattentional mechanisms associated with hypervigilance (Berman et al., 2002).

Sex differences in perceptual responses have been shown in IBS patients. Perceptual hypersensitivity to visceral stimuli is especially pronounced in female IBS patients (Chang et al., 2006b; Mayer et al., 1999). In contrast, male IBS patients show less visceral hypersensitivity than female patients but have greater sympathetic nervous system responses measured by skin conductance, and decreased cardiovagal activity measured by heart rate variability (HRV) com-

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pared to female IBS patients (Tillisch et al., 2005) and male controls. These sex differences have been hypothesized to reflect differential sensitivity of prefrontal and limbic arousal circuits underlying symptom generation in male and female IBS patients respectively (Labus et al., 2008; Naliboff et al., 2003), and analogous findings have recently been reported from functional brain imaging studies in the rat (Wang et al., 2009). We speculate that in terms of basic attentional processes, male IBS patients may therefore show poorer attentional control [associated with decreased vagal tone (Thayer and Brosschot, 2005)] compared to female IBS, and that the pronounced hypervigilance in female IBS might be associated with increased cognitive modulation of attention, reflected in greater symptom-related anxiety or response bias.

The acoustic startle response (ASR) is a fast defensive response to an intense exteroceptive stimulus, measured in humans via the eyeblink reflex. A simple neural circuit is known to mediate the startle reflex (Davis et al., 1982; Koch, 1999) but the modulation of this reflex based on affective state and other information processing demands has resulted in the startle reflex being highly useful as a non-invasive measure of central mechanisms. While the brain areas that mediate sensorimotor gating are in the pons, anterior cingulate and lateral prefrontal cortices provide 'top down' influence on this process via the thalamus (Campbell et al., 2007). These brain regions play an important role in modulation of pain and affect. Changes in the startle reflex following brief non-startling stimuli, prepulse inhibition of startle, has been widely used as a neurophysiological measure of the early pre-attentive stages of information processing and as an operational measure of sensorimotor gating and its top down modulation (Braff and Geyer, 1990; Braff et al., 2001; Cadenhead et al., 1999). Prepulse inhibition (PPI) of startle is the normal unlearned suppression of the startle reflex when the intense startling stimulus is immediately preceded (30–300 ms) by a weak nonstartling stimulus (the prepulse). PPI represents a general ability to inhibit responses to external (auditory, visual, tactile) and internal (thoughts, impulses) stimuli (Geyer et al., 1990). Sex differences and menstrual cycle effects have been repeatedly demonstrated in prepulse modulation of startle, with healthy women exhibiting less PPI than healthy men and reduced PPI in the luteal compared to the follicular phase of the menstrual cycle (Jovanovic et al., 2004; Swerdlow et al., 1993, 1997).

Although earlier research using prepulse modulation of startle has focused on information processing deficits in schizophrenia, many studies have now shown deficits in PPI in patients with other psychiatric disorders (reviewed in Braff et al., 2001), notably anxiety disorders including panic disorder (Ludewig et al., 2002) and post-traumatic stress disorder (Grillon et al., 1996) and obsessive compulsive disorder (Hoenig et al., 2005). More generally, a decreased PPI has been hypothesized to occur in disorders that involve a deficit in inhibition of responding to unimportant sensory, cognitive or interoceptive input (Swerdlow et al., 1995).

Although there have been no prior studies of PPI in patients with IBS or other functional somatic symptoms, one study of healthy individuals found *enhanced* PPI in subjects scoring higher on the 'Hysteria' scale of the MMPI, a scale associated with increased functional somatic symptoms and suppression of negative affect (Swerdlow et al., 1995). This suggests that at least in healthy subjects, somatic hypervigilance may be associated with the opposite effect on PPI from anxiety and ruminative disorders. In addition, PPI has been shown to be enhanced if subjects are given instructions that increase awareness/attention to the prepulse, are under conditions of threat, or if the prepulse itself is negative valenced (Aitken et al., 1999; Cornwell et al., 2008; Dawson et al., 1993; Filion et al., 1993; Schell et al., 1995).

The current study was designed to test if IBS patients show a lack of sensorimotor inhibition compared to healthy controls as evidenced by a *deficit* in PPI, or if they show increased PPI due to generalized hypervigilance. Since sex differences have been found both in studies of PPI and in IBS, the current study also examined sex differences in these responses. The following specific hypotheses were addressed:

1. IBS patients would generally show decreased PPI reflecting difficulty inhibiting responses to irrelevant stimuli (including physiological visceral stimuli), a concept previously suggested by lack of P50 habituation.
2. In addition, male and female IBS patients would show differing PPI responses compared to their same sex controls. Specifically, female IBS patients would show less reduction or even increases in PPI relative to female controls due to increased hypervigilance, while males would show greater declines in PPI compared to male controls.

2. Methods

2.1. Participants

A sample of 86 subjects with IBS (62 female) and 61 healthy controls (36 female) were recruited by advertisement. IBS diagnosis was confirmed using Rome II criteria during a clinical exam by a gastroenterologist or nurse practitioner experienced in functional GI disorders (Thompson et al., 1999). Bowel habit predominance was based on the Rome II supportive symptoms. Inclusion criteria for all subjects were: (1) no current use of psychoactive medication; (2) no current or past psychotic, major depressive, or substance abuse disorder; (3) no major medical conditions as determined during the clinical exam (with the exception of IBS for the IBS group). All study protocols were performed after approval by the UCLA and V.A. Greater Los Angeles Health Care System Institutional Review Boards. Informed consent was obtained from all subjects.

2.2. Stimuli

The startle stimulus consisted of a 50 ms burst of white noise at 105 dB SPL with a 0 ms rise time presented binaurally through stereophonic earphones. No masking noise was used; the ambient background noise varied between 30 dB and 35 dB SPL. For each trial, startle stimuli were presented either alone (Startle Alone), or preceded by a 25 ms 1000 Hz tone at 75 dB SPL with 4 ms rise and fall times and onset 120 ms before the startle stimulus onset (Prepulse) or by a continuous tone for 2000 ms.

2.3. Data acquisition

Electromyogram (EMG) activity of the orbicularis oculi was recorded from electrodes placed beneath the right eye approximately 10 mm apart edge to edge, and 8 mm below the lower lid margin. The medial electrode was placed directly under the pupil. A ground electrode was placed in the center of the forehead. The impedance level of the electrodes was 20 kΩ or less. EMG activity was recorded with a sampling rate of 1 kHz and was full-wave rectified with low and high frequency cut-off values of 30 Hz and 1 kHz, respectively. A vertical electro-oculogram (EOG) was recorded from electrodes placed above and below the left eye to monitor lid position, spontaneous blinking, and vertical saccades. The vertical EOG was used to control delivery of stimuli and in data preprocessing as discussed below. Data acquisition was performed with a Grass Instruments 15RX1 isolated physiodata amplifier system interfaced with a PC computer via a National Instruments BMC 2090; Multifunction Board. Custom programming using Labview® (National Instruments, Austin, TX, USA) software controlled all aspects of data acquisition, auditory and visual stimuli presentation and experimental timing. Separate custom programs were used for data screening and analysis.

2.4. Procedure

Prior to beginning the study, subjects with IBS were asked to rate the overall severity of their usual gastrointestinal symptoms on a numerical rating scale of 0 (no symptoms) to 20 (the most intense symptoms imaginable).

Following electrode placement, subjects were seated upright in a sound attenuated room adjacent to the experimental room, interconnected via intercom and closed-circuit video camera that provided a view of the subjects from two angles. Behavioral observations permitted identification of trials involving excessive body movements or drowsiness for data inspection and rejection if necessary.

Subjects were fitted with the headphones and watched a muted movie while they received the startle stimuli and prepulses. There was no instruction either to pay attention to or to ignore the sounds. Specifically, subjects were told that from time to time, they would hear some loud sounds and soft sounds through the headphones but that they did not have to say or do anything. All subjects received the same order of startle trials based on a Latin square design. The first and last trials consisted of a startle stimulus presented alone and were not included in analyses.