International Journal of Psychophysiology 80 (2011) 182–191

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Sex differences in the neural correlates of autonomic arousal: A pilot PET study

Allison C. Nugent [a,*], Earle E. Bain [b], Julian F. Thayer [c], John J. Sollers [d], Wayne C. Drevets [e]

[a] Section on Neuroimaging in Mood and Anxiety Disorders, NIMH/NIH, 9 Memorial Drive, MSC 0940, Bethesda, MD 20892-0940, United States
[b] Neuroscience and Anesthesia Development, Abbott Laboratories, Abbott Park, IL, United States
[c] Department of Psychology, The Ohio State University, Columbus, OH, United States
[d] Department of Psychological Medicine, The University of Auckland, Auckland, New Zealand
[e] Laureate Institute for Brain Research, Oklahoma University College of Medicine, Tulsa, OK, United States

ARTICLE INFO

Article history:
Received 29 September 2009
Received in revised form 23 February 2011
Accepted 1 March 2011
Available online 15 March 2011

Keywords:
Autonomic
HRV
PET
Sex
Amygdala

ABSTRACT

Electrophysiology, behavioral, and neuroimaging studies have revealed sex-related differences in autonomic cardiac control, as reflected in measurements of heart rate variability (HRV). Imaging studies indicate that the neurobiological correlates of autonomic nervous system (ANS) function can be investigated by measuring indices of HRV during the performance of mildly strenuous motor tasks or mildly stressful cognitive tasks. In this preliminary study, fifteen male and seven female healthy subjects underwent $H_2^{15}O$-positron emission tomography (PET) and electrocardiograph (ECG) recording while performing a handgrip motor task and an n-back task. Indices of HRV were calculated and correlated with regional cerebral blood flow (rCBF). We hypothesized that sex differences would be evident in brain regions known to participate in autonomic regulation: the anterior insula, the anterior cingulate cortex, the orbitofrontal cortex, and the amygdala. Our study found that associations between rCBF and parasympathetic indices differed significantly between female and male subjects in the amygdala. Females showed a positive correlation between rCBF and parasympathetic indices while males exhibited negative correlations. This differential correlation of amygdala rCBF and parasympathetic activity between males and females may reflect differences in parasympathetic/sympathetic balance between sexes, consistent with known sexual dimorphism in the amygdala and closely related structures such as the hypothalamus. These preliminary imaging results are consistent with earlier reports of significant correlation between brain activity and HRV, and extend these findings by demonstrating prominent sex differences in the neural control of the ANS. While the generalizability of our results was limited by the small size of the study samples, the relatively robust effect size of the differences found between groups encourages further work in larger samples to characterize sex differences in the neural correlates of autonomic arousal.

Published by Elsevier B.V.

1. Introduction

Numerous studies in humans suggest differences in autonomic cardiac control between the sexes. For instance, under arterial occlusion, females are more likely to exhibit brachycardia and a lowering of blood pressure, an essentially cardioprotective response, than males (Airaksinen et al., 1998). Under ischemic challenge, males exhibit a pressor response, while females exhibit either a decrease or no change in arterial pressure (Maixner and Humphrey, 1993). Females also exhibit blunted increases in mean arterial pressure and muscle sympathetic nerve activity during a head-up tilt postural challenge as compared to men (Shoemaker et al., 2001). In males, an acute lower body negative pressure (LBNP) challenge, which acutely lowers blood pressure in the upper body, activates baroreceptors, induces catecholamine release, and activates pressor responses, whereas females show an attenuated physiological response (Kimmerly et al., 2007). Taken together, these reports and others indicate greater reactivity of the parasympathetic system in females, and greater reactivity of the sympathetic nervous system in males (reviewed in Dart et al., 2002).

Abbreviations: ACC, anterior cingulate cortex; ACe, central nucleus of the amygdala; ANS, autonomic nervous system; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; BOLD, blood oxygen level dependent (fMRI contrast mechanism); ECG, electrocardiograph; fMRI, functional magnetic resonance imaging; HR, Heart rate; HRV, heart rate variability; IBI, inter-beat interval; LBNP, Lower body negative pressure (autonomic challenge); lnHF, Natural log of high frequency power of the heart rate spectrum. An indicator of parasympathetic activation; lnLF, Natural log of low frequency power of the heart rate spectrum. Partially dependent on sympathetic tone, but strongly dependent on parasympathetic activity as well; LF/HF, Ratio of low to high frequency power, generally used as an index of the balance of sympathetic to parasympathetic tone; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PET, positron emission tomography; PFC, prefrontal cortex; rCBF, regional cerebral blood flow; RMSSD, Root mean square standard deviation of successive R-R intervals of the heart rate time series. An index of parasympathetic tone; ROI, region of interest; STG, superior temporal cortex.

* Corresponding author. Tel.: +1 301 451 8863, +1 301 408 8560 (mobile); fax: +1 301 480 4684.
E-mail address: nugenta@mail.nih.gov (A.C. Nugent).

0167-8760/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.ijpsycho.2011.03.001

Interestingly, the sex differences in autonomic response to LBNP cited above were associated with differences in hemodynamic response measured with functional magnetic resonance imaging (fMRI). Men showed larger increases than women in blood oxygen level dependent (BOLD) contrast during the LBNP challenge in the right insula and dorsal anterior cingulate, and also showed larger decreases than women in BOLD contrast during the challenge in the right amygdala, left insula, ventral anterior cingulate, and ventral medial prefrontal cortex. A recent functional MRI study by Wong et al. (2007) found that during the performance of a handgrip task, women exhibited less activation in the insular cortex and dorsal cingulate than men. In the same study, heart rate (HR) and mean arterial pressure responses during the handgrip task were measured in a separate session and also found to be blunted in the women as compared to the men. The functional anatomical basis for sex-differences in autonomic regulation is rarely investigated, however, as most previous neuroimaging studies either limited their subject samples to one sex (Critchley et al., 2000; Lane et al., 2001), or did not directly assess sex effects in samples which combined males and females (Critchley et al., 2003; Matthews et al., 2004; Neumann et al., 2006).

Neuroimaging studies not examining sex implicate a specific network of regions involved in autonomic control, although distinct regions may be more involved in specific behavioral domains. Hemodynamic activity in the anterior cingulate cortex (ACC) and insula correlates with autonomic responses in a variety of behaviors (reviewed in (Critchley, 2005)). The ACC appears to be directly involved in autonomic control, although whether it generates or simply reflects autonomic state has not been established. It has also been suggested that the insula stores a visceral representation of the current autonomic state, particularly in response to emotional stimuli (Critchley, 2005). Similarly, the orbito-frontal cortex (OFC) appears to support a representation of autonomic state during motivational tasks (reviewed in (Nagai et al., 2004)). Neurophysiological activity in the amygdala strongly correlates with autonomic responses during highly emotional situations, such as fear conditioning (reviewed in (Critchley et al., 2005)). Additionally, multiple lines of research in experimental animals implicate the amygdala in sympathetic activation occurring in response to acute stress (reviewed in (Salome et al., 2007)). Furthermore, both animal and human lesion studies have shown that subjects with amygdalar lesions exhibit blunted autonomic responses to stress (reviewed in (Davis and Whalen, 2001)). Finally, retrograde labeling studies in experimental animals, implicate the amygdala, along with cingulate gyrus, insular cortex, and orbito-frontal cortex, as regions involved in both parasympathetic and sympathetic cardiac control (Ter Horst et al., 1996; Westerhaus and Loewy, 2001).

There is substantial evidence from the literature indicating that mildly effortful or stressful tasks also result in autonomic arousal, or activation of the ANS, and activation of brain areas known to be involved in autonomic control in humans. For example, activity in the amygdala has been associated with autonomic function during performance of a handgrip task, (Napadow et al., 2008), while activity in the ACC, OFC, and insula has been associated with cardiovascular arousal during both a handgrip task and an n-back cognitive task (Critchley et al., 2003). Given these results, we hypothesized that differences in autonomic responses between sexes would be related to underlying differences in activation in the ACC, insula, OFC, and amygdala.

Of these regions, the amygdala is a known site of sexual dimorphism (for example, (Cooke and Woolley, 2005; Simerly, 2002; Stefanova and Ovtscharoff, 2000)). Studies in rats have shown concentrations of estrogen receptors in the amygdala (Milner et al., 2008), while neuroimaging studies in humans have demonstrated alterations of amygdalar connectivity in response to testosterone (van Wingen et al., 2010). The hypothesis that sexual dimorphism in the amygdala may influence autonomic control is also supported by Labus et al. (2008) who found sex-related differences in amygdalar effective connectivity in response to aversive rectal distension in patients with irritable bowel syndrome. Projections to the central nucleus of the amygdala (ACe) are modulated by both vasopression (involved in anxiety, stress, and aggression) and oxytocin (involved in bonding and trust behaviors) (Debiec, 2005; Raggenbass, 2008). Vasopressin has been hypothesized to play a role in mediating the “fight or flight” response pattern seen particularly in men in response to stress, while oxytocin has been hypothesized to play a role in mediating the “tend and befriend” reaction seen more often in women in response to stress. It thus may be hypothesized that alterations in amygdalar function may underlie differential responses to stress between sexes (Taylor et al., 2000).

In the current pilot study, we investigated autonomic function in men and women by measuring indices of heart rate variability (HRV). A spectral decomposition of an ECG time series can be divided into frequency bands. The high frequency (HF) component, which is mediated almost entirely by parasympathetic activity transmitted via the vagus nerve (Akselrod et al., 1985; Pomeranz et al., 1985) is calculated as the total spectral power between 0.15 and 0.5 Hz. The peak frequency within this band, fHF, is proportional to the respiratory frequency (Thayer et al., 2002; Yildiz and Ider, 2006). The low frequency component (LF), which partially reflects sympathetic tone (Malliani and Pagani, 1991; Malliani et al., 1994), but is dominated by parasympathetic tone (Thayer et al., 2008) and respiration (Yildiz and Ider, 2006), is calculated as the total power between 0.01 and 0.15 Hz. The ratio LF/HF is often used as a measure of the relative balance of sympathetic and parasympathetic tone (Malliani et al., 1990), although it is an imperfect measure since LF and HF are often highly correlated. The time domain parameter RMSSD is also used as a measure of parasympathetic tone, and is calculated as the root mean squared difference of successive R-R intervals as a measure of beat-to-beat variability (Bigger et al., 1993; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Thus, indices of HRV can be used to examine both parasympathetic and, albeit imperfectly, sympathetic tone, and these measures can be correlated with imaging data to explore relationships between brain activity and autonomic control.

To test the hypothesis that the regions described above as part of our *a priori* hypothesis play a role in sex differences in ANS function, we measured indices of heart rate variability (HRV) to assess autonomic arousal, while also measuring regional cerebral blood flow (rCBF) using $[^{15}O]H_2O$-positron emission tomography (PET) in 15 male and 7 female healthy subjects. We obtained these measures both at baseline and during the performance of motor and cognitive tasks to examine the differential autonomic and neurophysiological responses to stress. Although the small sample sizes restrict the weight of our conclusions, this is the first study to examine central gender differences in autonomic control in response to mild stress using neuroimaging.

2. Materials and methods

2.1. Subjects

Participants included twenty-two right-handed (one female self-identified as having “mixed handedness”), medically healthy individuals (N = 22), of which fifteen were male (N = 15), and seven were premenopausal females (N = 7). Of the male subjects, 11 (73%) were Caucasian, with the remaining being African American (N = 3, 20%) or Hispanic (N = 1, 7%). Of the female subjects, 4 (57%) were Caucasian, with the remaining being African American, Hispanic, or Asian (N = 1, 14.3%, in each of the three groups). Subjects were recruited through IRB approved print advertisements. Although data was not collected on all subjects, men and women for which data was collected did not differ on IQ (N = 13) or socio-economic status (N = 14).