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Sex differences in anterior cingulate cortex activation during impulse inhibition and behavioral correlates

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ABSTRACT

Poor impulse inhibition is associated with behavioral problems including aggression and violence as well as clinical diagnoses such as attention deficit hyperactivity disorder (ADHD) and substance abuse, all of which are more prevalent in men than in women. Studies have found that fronto-parietal and fronto-striatal-thalamic networks are critical for successful impulse inhibition. However, few studies have investigated neural differences in these networks between men and women. In this study, we use a well established behavioral task, the parametric Go/noGo task, to explore the relationships between brain regional activity during impulse control and impulsivity trait measures, as well as sex differences in these relationships. We found that males showed heightened activation of the rostral anterior cingulate, which correlated with ratings related to impulsivity. We also found that the activation/deactivation in males and females correlates with personality ratings in a sex-specific manner.

1. Introduction

Impulse inhibition is a process involved in the suppression of behavior that is prepotent, overlearned or inappropriate (Aron et al., 2007). Poor impulse inhibition has been found to be a general liability factor for a range of externalizing and substance use problems including substance abuse, aggression and violence (Fillmore and Rush, 2002; Goldstein and Volkow, 2002; Monterosso et al., 2005; Magid et al., 2007; Young et al., 2009), and attention-deficit hyperactivity disorder (ADHD) (Crosbie and Schachar, 2001; Lijffijt et al., 2005; Rubia et al., 2005; Clark et al., 2007). These disorders are seen as part of a "disinhibitory psychopathology" including a variety of traits, all of which involve a deficit in self-control (Sher and Trull, 1994).

Sex difference in impulse inhibition and in related disinhibitory psychopathologies have been widely documented at the behavioral level. For example, ratings of impulsivity and risk-taking behavior are higher in men than in women (Labouvie and McGee, 1986; Campbell and Muncer, 2009) and this personality factor seems to be related to a sex difference in emotional regulation and aggression (Struber et al., 2008; Campbell and Muncer, 2009). Furthermore, disorders characterized by poor impulse inhibition are more prevalent in males than females, including substance use disorders, ADHD and conduct disorder (Kessler et al., 2005; Newman, et al., 2005; Eme, 2007; Struber et al., 2008). The specific relationship between impulsivity and the development of psychopathology may also be sex dependent. For example, although alcohol use is correlated with impulsivity in both males and females, this correlation is stronger in males (Stoltenberg et al., 2008). In addition, impulsivity is correlated with alcohol and caffeine use, not nicotine, in males; whereas females show a correlation between impulsivity and alcohol and nicotine use, but not caffeine (Waldeck and Miller, 1997). These data suggest that the brain mechanisms involved in impulse inhibition function in a somewhat sex specific manner. An understanding of sex differences in brain activity during impulse inhibition would therefore not only facilitate our understanding of the brain mechanisms of behavioral inhibition, but also elucidate the basis of different manifestations in males and females of a variety of behavior such as substance abuse and aggression.

A frequently used approach to the study of impulsivity is the use of a "go/no-go" paradigm. This paradigm engages individuals in responding to frequent "go" (target) signals and occasionally requires them to inhibit the response when an infrequent "no-go" (non target) signal occurs. This task examines the ability to inhibit a prepotent tendency to respond. Imaging studies in human subjects have shown activation of a primarily right-hemisphere network, including the ventral prefrontal cortex, the dorsolateral prefrontal cortex, parietal cortex and areas of the anterior cingulate (ACC) and the striatum during this task (Casey et al., 2001; Bunge et al., 2002; Simmonds et al., 2008).

There have been few imaging studies investigating sex differences in activation during response inhibition, with discrepant findings. For example, Li et al. (2006a) investigated impulse inhibition using a stop

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signal task and showed more extensive activation in males than in females during successful inhibition vs. failed inhibition in bilateral medial frontal cortex and cingulate cortex, globus pallidus, thalamus and parahippocampal gyrus. Furthermore, women were found to activate the caudate to mediate response inhibition whereas men activated medial superior frontal and anterior cingulate cortices (Li et al., 2006b). This suggests a sex difference in strategy for successful response inhibition. However, in a meta-analysis of five go-no-go studies, greater activation was found in females in almost all areas that showed sex difference in activations (Garavan et al., 2006). The discrepant findings between these studies may relate to the various probes utilized to examine these processes, and indicate the need for additional study. Here we used a Go/noGo task to examine neural circuits engaged during impulse inhibition, and identified brain areas activated during different trial types—Go trials, correct noGo trials and failed noGo trials. We then tested for the presence of sex differences of such activation and explored the relationship between neural responses and personality trait ratings related to impulsivity. It was hypothesized that differences would emerge in the magnitude of activation in brain areas involved in prepotent response inhibition, and in the relationship between these regions and personality ratings in males and females.

2. Methods

2.1. Participants

Healthy subjects (15 females and 13 males) participated in the study, ranging from 20 to 38 years of age (mean 25). They were medication-free, had no personal history of medical, psychiatric illness, substance abuse or dependence and no family history of inheritable medical or psychiatric illnesses. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders DSM-IV nonpatient version was used to rule out undiagnosed psychiatric illness and substance abuse (First et al., 1995). Participants did not take psychotropic medications or hormone treatments, including birth control in women, for at least 6 months, were nonsmokers, and did not exercise in excess of 1 h three times a week nor were involved in competitive exercise. All participants signed an informed consent after explanation of experimental protocol, as approved by the University of Michigan Institutional Review Board.

2.2. Personality trait measures

Subjects completed the Zuckerman–Kuhlman Personality Questionnaire (ZKPQ) (Zuckerman and Kuhlman, 1993) and NEO Personality Inventory (NEO-PI-R) (Costa and McCrae, 1992). The ZKPQ questionnaire uses 89 true/false statements to measure five facets of personalities: impulsive sensation seeking, neuroticism-anxiety, aggression-hostility, activity, and sociability. We used Form S (self rated form) of NEO-PI-R, which contains 240 questions and measures five facets of personality: neuroticism, extraversion, openness, agreeableness, conscientiousness.

2.3. Impulse inhibition task

We employed a commonly used behavioral task that measures motor impulse inhibition. The "Go/noGo" task requires a motor response from the subjects to the "Go" signal, and the withholding of the motor response to occasional "noGo" signals. Each subject performed 245 trials divided into five consecutive runs. Each trial lasted 4 s. At the beginning of each trial, a letter is shown at the center of the screen for 0.5 s, followed by 3.5 s of a fixation point. Subjects were instructed to press the response key as quickly as possible if the letter was not "X", and to do nothing if the letter was "X". The letter "X" appeared in 60 of the 245 trials, each preceded by either one, three or five nonX letters and the order of the trials was pseudo-randomized (Durston et al., 2002). Both the response and response time were recorded.

2.4. fMRI data acquisition

Whole-brain blood-oxygen-level-dependent (BOLD) signal was acquired using a 3.0Tesla GE Signa system (Milwaukee, WI) and a standard radio frequency coil. A T2*-weighted sequence was used with the following parameters: single-shot combined spiral in/out acquisition (Glover and Law, 2001), gradient echo, repetition time (TR) = 2 s, echo time (TE) = 30 ms, flip angle = 90°, field-of-view (FOV) = 20 cm, matrix size = 64 × 64, slice thickness = 3 mm with no gap. 30 axial slices were taken. The duration of the scan matched the duration of the task. Anatomical scans for the purpose of cortical area localization were performed with a T1-weighted high-resolution sequence: 3-dimentional spoiled gradient recalled echo (3-DSPGR), TR = 25 ms, minimum TE, FOV = 24 cm, matrix size = 256 × 256, slice thickness = 1.4 mm. Visual stimuli were presented using the integrated functional imaging system (Psychology Software Tools, Inc., Pittsburg, PA). An LCD display was used in the bore of the MR scanner. Motor responses were recorded through a fiberoptic response collection device. We used foam pads around the head along with a forehead strap to minimize subjects' head movement in the scanner.

2.5. Data analysis

2.5.1. Behavioral responses

We defined trials in which subjects withheld response to X as "correct noGo" trials, those in which subjects responded to X as "failed noGo" trials. The vast majority of subjects did not fail to make a motor response in any trials with nonX letters, and consequently all nonX trials were included in the analyses (Go trials). We defined the accuracy as the number of correct noGo trials divided by the number of noGo (letter X) trials. The reaction time was computed as the average reaction time during the failed noGo trials.

2.5.2. fMRI data analysis

Standard preprocessing was performed on the images: 10 s of data at the beginning of each block was discarded to allow scanner saturation; images were slice time corrected, realigned and smoothed with SPM2 using a 5 mm Gaussian filter (Wellcome Institute of Cognitive Neurology, London, UK). Subsequent analyses were performed with SPM2. A General Linear Model was constructed with the correct noGo trials, failed noGo trials and Go trials across all five runs as epochs and the movement parameters collected during scanning as regressors. The linear contrasts that we computed include 1) correct noGo vs. Go trials, 2) failed noGo vs. Go trials, and 3) correct noGo vs. failed noGo. The contrast *t*-maps of individual subjects were coregistered with the T1 anatomical images, and normalized with the Montreal Neurological Institute (MNI) template. We examined the contrast images at the group level and areas that showed activation or deactivation are defined as those that included at least 10 voxels with $p<0.05$ after FDR correction for multiple comparisons, adjusting for the size of the cluster under consideration. "Activation" and "deactivation" refer to the activation level in comparison to the control condition, instead of absolute level of activation. Sex differences were tested with two-sample *t*-tests with correction for multiple comparisons and at least 10 voxels in extent.

2.5.3. Region of interest (ROI) analysis

The activated and deactivated areas identified in the main contrasts were used to define ROIs and the ROIs were extracted using the Marsbar toolbox in SPM2 (Brett et al., 2002). The main analyses with these ROIs were their correlation with personality trait ratings and task performance. For each subject and each ROI, we