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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 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.

Keywords

impulsivity; fMRI; impulsivity trait measure; Go/noGo task

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).

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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. (2006) investigated impulse inhibition using a stop signal task and showed more extensive activation in males than females during successful inhibition versus 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., 2006). 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 seconds. At the beginning of each trial, a letter is shown at the center of the screen for 0.5 second, followed by 3.5 seconds 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 (Durstun 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) = 2s, echo time (TE) = 30ms, flip angle = 90°, field-of-view (FOV) = 20cm, matrix size = 64×64, slice thickness = 3mm 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-dimensional spoiled gradient recalled echo (3-DSPGR), TR = 25ms, minimum TE, FOV = 24cm, matrix size = 256×256, slice thickness = 1.4mm. 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 seconds 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 5mm 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 obtained an average beta value for each trial condition (correct noGo - Go, failed noGo - Go, correct noGo - failed noGo) as the approximation of the level of modulation. We then computed the correlation between the modulation and the accuracy and the average reaction time of each subject. We also calculated the correlation between the modulations and four personality trait measures that are related to impulsivity: impulsivity and sensation seeking (ZKPQ); impulsivity and excitement seeking (NEO-PI-R). We used Spearman rank correlation test for all the correlation calculations to circumvent any assumptions about the underlying distribution of behavior and the BOLD modulation. To correct for multiple testing and the possible correlation between beta values for different conditions, we constructed a “null distribution” by permutation. In each permutation, while keeping each subject's beta values in the original order, we randomly reassigned each set of behavioral measures (either accuracy or reaction time, or impulsivity trait measures) to a subject, then computed the correlation between betas in each condition and the reassigned behavioral measures. This process was typically repeated 1,000 times to construct a distribution of correlation coefficients for each beta-behavior pair. The *p* values of the correlation coefficients computed from the actual data were then determined using these constructed distributions. The analyses were conducted in Matlab (Mathworks, Inc., Natick, MA, USA) unless otherwise noted.

3. Results

3.1. Task performance

The accuracy ranged from 30 to 87%, (mean $\pm$ SD: 71 $\pm$ 3). Reaction times ranged from 273ms to 438ms (mean $\pm$ SD: 352 $\pm$ 7). Male and female subjects did not show difference in the accuracy (Mann-Whitney U test, $p = 0.43$). However, male subjects showed faster average reaction times (327ms) than female subjects (373 ms) (Mann-Whitney U test, $p < 0.001$). Correlation between reaction time and the accuracy approached significance (Spearman rank correlation test, $r = 0.34$, $p = 0.08$) across all subjects. Female or male subjects alone did not exhibit such correlation. Whether an X was preceded by one, three or five nonX letters did not affect task performance (one-way ANOVA, $p = 0.56$ for accuracy; $p = 0.46$ for reaction time).

Consistent with data in larger population samples reported in the literature, females, compared to males, showed lower ZKPQ impulsivity scores ($p < 0.05$). But there was no significant sex difference in sensation seeking ($p = 0.49$), NEO-PI-R impulsiveness ($p = 0.39$) or excitement seeking ($p = 0.26$).

3.2. Group activation

All contrasts that are presented in the results are differential contrasts. We examined regional activation during correct noGo compared to Go trials, failed noGo compared to Go trials, and correct noGo trials vs. failed noGo trials. We were particularly interested in the relationship between regional activity during response inhibition and inter-individual variation in traits related to impulsivity and behavioral inhibition/activation as measured with established personality inventories, an area poorly understood and not typically explored in the literature.

Group data from all subjects (Table 1) shows activation and deactivation patterns often observed during impulse control tasks. During correct noGo the activation is mostly in the right hemisphere. Deactivation includes some left hemisphere structures such as left middle temporal gyrus and precuneus, also the orbital frontal cortex (OFC). During failed noGo trials the activation includes bilateral inferior frontal gyri and the ACC; while deactivation includes widespread bilateral structures. When correct and failed noGo trials are directly contrasted, structures that are more activated in correct than in failed noGo trials include right middle temporal and precentral gyri, supplementary motor area, bilateral superior and middle occipital gyri and putamen. Structures that are more activated in failed than in correct noGo trials include the ACC, left inferior frontal gyrus, insula and lingual gyrus.

3.3. Sex differences in impulse control circuitry

Female and male subjects, when examined alone, showed that they contributed differentially to the activations/deactivations seen in all subjects (Table 2A and 2B). The subset of activations/deactivations that female subjects contributed to include the right inferior temporal gyrus during correct noGo activation; superior frontal gyrus and precuneus during correct noGo deactivation; the ACC, the inferior frontal gyrus, insula and the supramarginal gyrus during failed noGo activation; the occipital cortex, the OFC, middle temporal and middle frontal gyri during failed noGo deactivation; occipital cortex when correct noGo is contrasted to failed noGo; and the ACC and the inferior frontal gyrus when failed noGo is contrasted with correct noGo.

When male subjects were examined alone (Table 2B), they contributed to the middle temporal gyrus deactivation during correct noGo; inferior frontal gyri during failed noGo activation; the occipital deactivation during failed noGo; putamen during correct noGo

contrasted with failed noGo; and the lingual gyrus during failed noGo contrasted to correct noGo.

We directly compared male and female activation/deactivation (two-sample t test, Table 2C and 2D, Figure 1). A significant difference was observed in the ACC (BA 32). For the ACC, there is a greater magnitude of activation in males than females in 1) correct noGo trials vs. failed noGo trials; and 2) correct noGo vs. Go trials. Given that females were less impulsive than males in our sample when measured with ZKPQ, we investigated whether the differential activation of ACC can be accounted for by sex differences in impulsivity. Using impulsivity ratings from ZKPQ scales as covariates, we did regression analysis and the sex difference in ACC activation remained significant (for correct noGo vs. Go trials, $p = 0.04$ with ZKPQ scores as covariate; for correct vs. failed noGo, $p = 0.04$ with ZKPQ scores as covariate). The only other area that showed sex difference is the middle temporal gyrus (BA 39), it is more activated in females than in males when correct noGo is contrasted with failed noGo.

3.4. Correlation with task performance

Based on the activation and deactivation patterns that we observed in the group analysis (Table 2), we examined the correlation between ROI modulation and subjects' task performance (accuracy and reaction time). Note here that a negative correlation between accuracy and deactivation means that the more deactivation, the higher the accuracy; and a negative correlation between reaction time and deactivation means that the more deactivation, the slower the reaction time.

For male subjects, a number of brain areas correlated with task performance accuracy (Table 3A). Better accuracy was positively correlated with more activation of the putamen, caudate nucleus in the correct trials, and BA18 of the occipital cortex in the failed noGo trials. Better accuracy was also correlated with more deactivation of superior frontal and superior occipital cortex and putamen during failed noGo. Faster reaction time was correlated with more occipital activation during correct noGo, which might reflect the effect the sensory processing.

For female subjects (Table 4A), better performance was correlated with more activation of the right inferior temporal gyrus and less activation of precuneus during correct noGo. Slower reaction time was correlated with more activation of inferior and middle temporal gyri during correct noGo or correct vs. failed noGo. Slower reaction time was also correlated with more occipital deactivation.

Comparing the correlation between ROI modulation and task performance in males and females, it is worth noting that both males and females showed the same trend of having positive correlation between task accuracy and ROIs that are activated during the noGo trials, and negative correlation between task accuracy and ROIs that are deactivated during noGo trials. The same trend is seen for the correlation between reaction time and task performance as well.

Areas that showed sex differential activation showed different correlation with reaction time, and only with male subjects (Table 5). More ACC activation during correct noGo trials, and less BA39 activation when correct noGo was contrasted with failed noGo, were correlated with faster reaction time. Female subjects did not show even a weak trend of correlation between the modulation of these ROIs and task performance.

3.5. Correlations with impulsivity, behavioral inhibition and activation trait measures

In this analysis, we determined the correlation between ROI modulation and personality trait ratings related to impulsivity. As above, a negative correlation between ratings and a deactivated area reflects that the more deactivation, the higher the ratings.

For male subjects (Table 3B), the ACC activation during correct noGo was negatively correlated with impulsivity. But the general trend was that brain areas that showed activation during failed noGo trials and when correct and failed noGo trials were contrasted were positively correlated with impulsivity and behavioral activation measures. Brain areas that were deactivated during both correct and failed noGo trials were generally negatively correlated with ratings of impulsivity and behavioral activation.

In contrast, female subjects did not show strong relationships between personality ratings and deactivated brain areas. Furthermore, brain areas activated during correct and failed noGo trials tended to show negative correlation with impulsivity and behavioral activation measures (Table 4B), which was opposite to the trend that we observed in male subjects.

The ACC region that was more activated in males during correct noGo showed a positive correlation with excitement-seeking in male subjects (Table 5). This is consistent with its correlation with faster reaction times. Female subjects, on the other hand, did not show any trend between the modulation of these ROIs and personality ratings.

4. Discussion

Our study focused on sex differences in brain activity during successful and failed impulse inhibition. We further investigated whether brain activation was correlated with task performance and traits indicative of impulsivity and behavioral inhibition and activation, and whether there were sex differences in these correlations. We found significant sex difference during impulse control in the ACC (males>females) and the middle temporal cortex (females>males). Furthermore, males showed a positive correlation between ACC activation and ratings of excitement-seeking, which was not observed in females.

Overall, the combined group of males and females showed a pattern of activation consistent with those observed in previous studies (e.g., Garavan et al., 1999; Liddle et al., 2001; Aron and Poldrack, 2006)– a primarily right-hemisphere fronto-parietal network. Deactivations were found mainly in the bilateral posterior parietal and inferior frontal regions, as previously reported (Hester et al., 2004; Tapert et al., 2007). Stevens et al. (Stevens et al., 2007) investigated functional neural networks underlying response inhibition and found an inhibitory influence of three distinct circuits on one another based on task demands. Therefore, successful inhibition requires both activation of task-related brain regions and deactivation of irrelevant brain regions. This has been proposed for cognitive tasks more generally, with the default mode network (DMN) reducing its baseline level of activity during effortful, task-relevant processing (Greicius et al., 2003; Raichle et al., 2001).

The only areas that showed significant sex difference during impulse control were the activations in the ACC (males>females) and the middle temporal cortex (females>males). We found heightened activation of the rostral ACC in males compared with females, during correct noGo trials compared to Go trials and during and during correct noGo trials compared to failed noGo trials. Furthermore, ACC activation was correlated with task performance and personality trait measures in males only. Males showed strong negative correlations between reaction time in the impulse inhibition task and ACC and a positive correlation with ratings of excitement-seeking.

The ACC has been implicated in conflict-monitoring, decision-making, and response inhibition e.g. (Isomura and Takada, 2004; Brown et al., 2006; Li et al., 2006). The right ACC, in particular, has been found to be related to errors during inhibition response (Menon et al., 2001; Brown et al., 2006). We observed its activation in all subjects when failed noGo trials were contrasted with Go trials. This is consistent with the rostral ACC playing a role in error processing (Kiehl et al., 2000). However, this pattern was different when data from male subjects were inspected alone. In male subjects the ACC was activated when correct noGo trials were contrasted to Go trials. Li et al. (2006) also observed the activation of ACC in male subjects during impulse control during a different impulse control task, the “stop-signal” task. Recent conceptualizations of the function of the ACC speculate a role beyond error detection, consistent with this finding in males. For example, Posner and colleagues (Posner et al., 2007) suggest the ACC is involved in self-regulation more broadly, acting as part of a network involved in orienting to control incoming information from the environment with the purpose of selecting appropriate responses. Similarly, Walton and colleagues (Walton et al., 2007) propose that the ACC is crucial to a distributed system that integrates current information with learned information regarding action value to guide adaptive decision making. Therefore, the strong correlation of ACC with task performance and excitement-seeking personality ratings in males as well as its sex-specific activation during impulse control suggest a sex difference in self-regulation. It has previously been shown that the ACC is more activated during inhibitory control in individuals who score high on a measure of dispositional impulsivity (Brown et al., 2006). The present results show this effect in males only, consistent with the fact that males typically rate themselves as more impulsive than females.

We also observed greater activation of the middle temporal cortex in females compared to males, when correct noGo was contrasted to failed noGo. This area has been implicated in impulse control tasks in previous literature (Garavan et al., 2006), but its function in impulse control remains unclear. However, in a study of attention, it was found that subjects with ADHD recruited the middle temporal gyrus less than comparison subjects (Shafritz et al., 2004). The authors suggest that this region is involved in attention to verbal stimuli, which may be deficient in those with lower impulse control. This is consistent with the direction of findings in the present study.

A number of brain areas showed significant activation/deactivation in females or in males alone, but their sex differential levels of activation/deactivation do not reach statistical significance after correction for multiple comparison. These areas nonetheless provide insight on how impulse control tasks might be carried out differently in males and females. Males and females showed similar trend in the correlation between ROI modulations and task performance: higher activation/deactivation during noGo trials correlate with higher accuracy and longer reaction time (less impulsive behavior). This highlights the importance of activating/deactivating appropriate brain regions during impulse control. However, females and males also showed different trends when we examined correlations between ROI modulations and personality ratings. Brain areas that are activated in males are generally positively correlated with impulsivity and behavioral activation measures, while areas deactivated tend to be negatively correlated with such measures. In contrast, brain areas in females that are activated tend to be negatively correlated with impulsivity and behavioral activation measures, while areas deactivated don't correlate with such measures. It is possible that these patterns of brain activation and deactivation during impulse control may reflect generally different processing strategies in males and females. For example, it might be more important for males to inhibit inappropriate response, but more important for females to elicit appropriate response. The one personality trait rating that showed correlations with ROI modulations that point to the opposite direction for both males and females is the impulsivity measure in NEO-PI-R. Close examination of the questions that

are used to rate this trait shows that it is likely to be measuring a different form of impulsivity (e.g. acting on cravings and urges rather than to delayed gratification) than the motor control impulsivity that we study in the Go-noGo task. Given our relatively small sample size, however, it is possible that some weak or moderate brain activity modulation was not detected. Furthermore, some potentially important correlations between brain activity modulation and behavioral measures may also go undetected. Further studies with a larger pool of subjects will be needed to confirm and extend our findings.

Deficits in impulse inhibition are related to a wide range of behavioral and clinical problems such as substance abuse, ADHD, violence and aggression. Many of these disorders are more prevalent in males than in females. Understanding the sex differences in brain activity during impulse inhibition therefore helps elucidate the neurobiological basis of these processes. Our study showed that ACC is a major locus exhibiting sex differential activation: greater activation in males during correct noGo trials and in correct vs. failed noGo trials. Interestingly, this area has been implicated in many behavioral and clinical problems that are more prevalent in males than in females. Hypoactivity of ACC has been observed during a variety of cognitive tasks in addicted individuals, and nicotine users (Kaufman et al., 2003; Goldstein et al., 2009; Hester et al., 2009). Such ACC hypoactivity is also present in ADHD individuals during cognitive tasks (Bush et al., 1999). ACC activity is also correlated with anger and aggression in healthy individuals (Denson et al., 2009) and has been shown to be reduced in Major Depression, a syndrome more prevalent in women than in men (e.g. Mayberg et al., 1997; Drevets et al., 2008). Our results are consistent with these findings and suggest an important role of ACC in the regulation of impulsivity and sex differences in pathological states where impulsivity plays a role.

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A. (-4, 42, 20). Correct noGo, M>F.

B. (2, 40, 20). Correct noGo – failed noGo, M>F.

C. (-58, -64, 6). Correct noGo – failed noGo, F>M.

Figure 1.

Activation differences between male and female subjects, and correlation between BOLD activity in ACC and impulsivity trait measures in male subjects. A. Greater ACC activation during correct Go trials in males. B. Greater ACC activation in males during correct noGo vs. failed noGo trials. C. Greater middle temporal activation in females during correct noGo vs. failed noGo trials.

Table 1

Summary of significant activation/deactivation clusters in all subjects. CnoGo: correct noGo; FnoGo: failed noGo.

Region (BA)	Volume (# of voxels)	MNI coordinates (x, y, z)	Peak T	p (corrected)	% mod. mean (ste)
<i>CnoGo activation:</i>					
R. inferior temporal gyrus (37)	758	66, -58, -8	5.12	0.011	0.12 (0.02)
Precuneus (7)	562	6, -64, 66	5.05	0.045	0.24 (0.05)
R. inferior frontal gyrus, opercular part (44)	495	60, 16, 0	5.01	0.076	0.20 (0.04)
R. Superior Frontal Gyrus (10)	958	32, 62, 16	4.87	0.003	0.16 (0.03)
R. superior temporal gyrus (22)	1143	66, -50, 20	4.71	0.001	0.13 (0.03)
<i>CnoGo deactivation:</i>					
L. and R. Precuneus (31)	7964	-16, -58, 14	6.93	<0.001	-0.10 (0.02)
Orbital frontal cortex (11)	1263	-2, 48, -22	5.94	0.001	-0.12 (0.02)
L. middle temporal gyrus (21)	689	-54, -12, -14	5.87	0.018	-0.10 (0.02)
<i>FnoGo activation:</i>					
R. inferior frontal gyrus, opercular and Orbital parts (44, 47)	3217	60, 14, 2	8.02	<0.001	0.29 (0.04)
Insula		44, 14, -2	7.96		
L. inferior frontal gyrus, orbital part. (47, 22)	1514	-44, 18, -8	7.88	<0.001	0.26 (0.02)
Cerebellum	871	-4, -84, -16	5.37	<0.001	0.23 (0.05)
Anterior cingulate (32)	791	0, 30, 26	5.15	0.001	0.23 (0.05)
R. supramarginal gyrus (40)	1236	64, -44, 32	5.07	<0.001	0.24 (0.05)
<i>FnoGo deactivation:</i>					
R. inferior temporal gyrus (37)	3169	42, -66, -10	7.83	<0.001	-0.16 (0.01)
Orbital frontal cortex (11)	2910	4, 48, -16	7.58	<0.001	-0.18 (0.02)
Middle occipital gyrus (19)	3206	-26, -86, 6	7.48	<0.001	-0.18 (0.02)
R. precentral gyrus (4)	898	40, -4, 48	6.40	<0.001	-0.16 (0.03)
Precuneus (30)	626	-10, -50, 12	6.00	<0.001	-0.20 (0.03)
L. supramarginal and angular gyri (7)	188	-26, -50, 46	5.91	<0.001	-0.16 (0.03)
L. inferior frontal gyrus, triangular part (46)	930	-42, 32, 14	5.80	<0.001	-0.15 (0.02)
L. middle temporal gyrus (21)	297	-58, -10, -8	5.64	0.002	-0.19 (0.03)
R. superior parietal gyrus (7)	211	22, -52, 54	5.63	0.014	-0.15 (0.03)
L. precentral gyrus (4)	190	-54, -2, 48	5.23	0.023	-0.21 (0.04)

Region (BA)	Volume (# of voxels)	MNI coordinates (x, y, z)	Peak T	p (corrected)	% mod. mean (se)
L. middle frontal gyrus (8)	934	-24, 28, 58	5.14	<0.001	-0.19 (0.03)
L. superior temporal gyrus (22)	184	-46, -38, 12	5.03	0.026	-0.14 (0.03)
<i>ChoiGo - FnoGo:</i>					
L. and R. superior and middle occipital gyrus (19)	2792	24, -84, 24	6.43	<0.001	0.17 (0.02)
supplementary motor area (6)	4125	-4, -10, 60	5.95	<0.001	0.18 (0.03)
R. precentral gyrus (4)	811	42, -8, 50	5.22	0.002	0.16 (0.03)
R. middle temporal gyrus (21)	596	66, -12, -8	5.07	0.01	0.18 (0.03)
Putamen	746	-22, 12, 0	4.96	<0.001	0.18 (0.04)
Putamen	639	26, 8, 6	4.86	0.007	0.17 (0.04)
<i>FnoGo - ChoiGo:</i>					
L. inferior frontal gyrus, orbital part (47)	1483	-46, 22, -8	5.59	<0.001	0.23 (0.03)
Insula	1539	44, 12, -4	5.49	<0.001	0.25 (0.04)
Anterior cingulate (32)	482	2, 30, 28	4.76	0.030	0.25 (0.06)
lingual gyrus (18)	946	6, -88, -10	4.47	0.001	0.21 (0.04)

Summary of significant activation/deactivation clusters when females and males were examined separately. CnoGo: correct noGo; FnoGo: failed noGo.

Table 2

A. Female subjects only.						
Region (BA)	Volume (# of voxels)	MNI coordinates (x, y, z)	Peak T	p (corrected)	% mod. mean (ste)	
<i>CnoGo activation:</i>						
R. inferior temporal gyrus	714	68, -34, 16	5.04	0.016	0.14 (0.02)	
<i>CnoGo deactivation:</i>						
Superior frontal gyrus (10)	953	-6, 58, -6	7.50	0.003	-0.15 (0.02)	
Precuneus (31)	1232	-6, 58, 26	5.66	0.001	-0.13 (0.02)	
<i>FnoGo activation:</i>						
L. inferior frontal gyrus orbital part (47)	685	-48, 20, -10	6.80	<0.001	0.36 (0.04)	
R. Middle frontal gyrus (10)	669	30, 56, 28	6.41	<0.001	0.33 (0.05)	
Insula	1243	46, 12, -2	6.15	<0.001	0.42 (0.07)	
Anterior cingulate cortex (32)	459	4, 42, 20	6.02	0.006	0.34 (0.08)	
Parietal supramarginal gyrus (40)	820	60, -44, 32	5.32	<0.001	0.33 (0.06)	
<i>FnoGo deactivation:</i>						
R. inferior occipital gyrus (18)	5253	32, -88, -6	8.46	<0.001	-0.20 (0.02)	
R. middle occipital gyrus (19)	5268	-40, -70, 24	8.10	<0.001	-0.18 (0.02)	
Orbital frontal cortex (11)	3718	4, 46, -16	7.24	<0.001	-0.20 (0.02)	
Middle temporal gyrus (21)	406	-56, -16, -10	6.73	0.012	-0.22 (0.04)	
Middle frontal gyrus (8)	663	-22, 22, 46	4.32	<0.001	-0.18 (0.04)	
superior frontal gyrus, dorsolateral (6)	566	-20, -10, 74	4.29	0.001	-0.20 (0.05)	
<i>CnoGo – FnoGo:</i>						
middle occipital gyrus (19)	1870	32, -88, 16	9.83	<0.001	0.22 (0.02)	
inferior occipital gyrus (19)	477	-50, -80, -14	8.53	0.018	0.20 (0.03)	
middle occipital gyrus (19)	4003	-28, -80, 34	6.69	<0.001	0.22 (0.03)	
middle temporal gyrus (39)	475	50, -68, 2	6.57	0.019	0.24 (0.05)	
<i>FnoGo – CnoGo:</i>						
inferior frontal gyrus, orbital surface (47)	346	52, 30, -6	5.53	0.081	0.48 (0.11)	
anterior cingulate cortex (32)	693	2, 42, 20	5.16	0.002	0.38 (0.09)	
inferior frontal gyrus, orbital part (47)	396	-50, 22, -10	4.23	0.045	0.34 (0.7)	

B. Male subjects only.						
Region (BA)	Volume (# of voxels)	MNI coordinates (x, y, z)	Peak T	p (corrected)	% mod. mean (se)	
<i>CnoGo activation:</i>						
Anterior Cingulate (32)	380	6, 38, 20	5.50	0.005	0.12 (0.02)	
<i>CnoGo deactivation:</i>						
inferior temporal gyrus (37)	394	-50, -54, -24	6.97	0.004	-0.09 (0.02)	
middle occipital gyrus (18 or 19)	1716	-20, -88, 14	6.59	<0.001	-0.12 (0.01)	
middle temporal gyrus (21)	307	-58, -10, -10	5.64	0.017	-0.11 (0.02)	
lingual gyrus (19)		18, -44, -2			-0.14 (0.03)	
<i>FnoGo activation:</i>						
inferior frontal gyrus, orbital part (47)	1671	36, 22, -16	13.46	<0.001	0.32 (0.03)	
inferior frontal gyrus, orbital part (47)	1022	-32, 18, -12	10.50	<0.001	0.28 (0.02)	
lingual gyrus (18)	253	14, -80, 0	6.10	0.045	0.26 (0.05)	
<i>FnoGo deactivation:</i>						
middle occipital gyrus (19)	1091	42, -76, 2	6.88	<0.001	-0.17 (0.02)	
superior occipital gyrus (19)	679	-26, -76, 42	6.63	<0.001	-0.22 (0.03)	
Putamen	185	26, 10, 6	5.59	0.17	-0.19 (0.04)	
Putamen	256	-28, 8, 0	6.61	0.043	-0.17 (0.03)	
superior frontal gyrus, dorsolateral (6)	380	-22, -4, 68	5.51	0.005	-0.24 (0.04)	
<i>CnoGo – FnoGo:</i>						
Putamen	400	26, 8, -10	5.51	0.003	0.23 (0.05)	
Caudate nucleus	443	-6, 18, -2	4.67	0.002	0.24 (0.05)	
<i>FnoGo – CnoGo:</i>						
inferior frontal gyrus, orbital part (47)	600	36, 20, -16	7.13	<0.001	0.27 (0.04)	
superior temporal gyrus (22)	818	-50, 0, 0	7.08	<0.001	0.27 (0.03)	
lingual gyrus (18)	312	20, -70, 0	5.37	0.015	0.25 (0.05)	
C. Males > Females.						
Region (BA)	Volume (# of voxels)	MNI coordinates (x, y, z)	Peak T	p (corrected)		
<i>CnoGo activation:</i>						
Anterior cingulate (32)	1233	-4, 42, 20	5.13	<0.001		
<i>CnoGo – FnoGo:</i>						
Anterior cingulate (32)	954	2, 40, 20	4.08	0.008		

D. Females > Males.				
Region (BA)	Volume (# of voxels)	MINI coordinates (x, y, z)	Peak T	p (corrected)
<i>CnoGo - FnoGo:</i>				
middle temporal gyrus (39)	782	-58, -64, 6	4.79	0.023

Table 3

Correlation between ROI modulation and task performance and personality trait measures, male subjects only. The ROI and its coordinates are defined as the activation/deactivation areas in males only, as described in Table 2B. The table lists the correlation coefficients with the p values in the parenthesis.

A. Correlation between ROI modulation and task performance (accuracy and reaction time).			
	Accuracy	Reaction time	
<i>CnoGo</i> deactivation:			
middle occipital gyrus (18 or 19), -20, -88, 14		-0.54 (0.05)	
lingual gyrus (19), 18, -44, -2		-0.45 (0.10)	
<i>FnoGo</i> activation:			
lingual gyrus (18), 14, -80, 0	0.49 (0.06)		
<i>FnoGo</i> deactivation:			
superior occipital gyrus (19), -26, -76, 42	-0.45 (0.11)		
Putamen, 26, 10, 6	-0.57 (0.03)		
Putamen, -28, 8, 0	-0.53 (0.06)		
superior frontal, dorsolateral (6), -22, -4, 68	-0.73 (0.002)		
<i>CnoGo</i> – <i>FnoGo</i> :			
Putamen, 26, 8, -10	0.48 (0.10)		
Caudate nucleus, -6, 18, -2	0.53 (0.06)		
<i>FnoGo</i> – <i>CnoGo</i> :			
lingual gyrus (18), 20, -70, 0	0.55 (0.03)		
B. Correlation between ROI modulation and personality trait measures.			
	NEO-PI-R		ZKPQ
	impulsivity	excitement-seeking	impulsivity sensation-seeking (ss)
<i>CnoGo</i> activation:			
Anterior Cingulate (32), 6, 38, 20	-1.0 (<0.001)		
<i>CnoGo</i> deactivation:			
inferior temporal gyrus, -50, -54, -24			-0.72 (<0.01)
middle occipital gyrus (18 or 19), -20, -88, 14			-0.63 (0.02)
<i>FnoGo</i> activation:			
inferior frontal gyrus, orbital part (47), -32, 18, -12			-0.63 (0.12)
lingual gyrus (18), 14, -80, 0		0.49 (0.09)	

B. Correlation between ROI modulation and personality trait measures.				
	NEO-PI-R		ZKPQ	
	impulsivity	excitement-seeking	impulsivity	sensation-seeking (ss)
<i>FnoGo deactivation:</i>				
middle occipital gyrus (19), 42, -76, 2				
superior occipital gyrus (19), -26, -76, 42		-0.45 (0.09)		-0.83 (<0.01)
Putamen, 26, 10, 6		-0.57 (0.01)		-0.45 (0.10)
Putamen, -28, 8, 0		-0.53 (0.04)		
superior frontal gyrus, dorsolateral (6), -22, -4, 68		-0.73 (0.004)		
<i>ChoGo – FnoGo:</i>				
Putamen, 26, 8, -10		0.48 (0.07)		0.60 (0.08)
Caudate nucleus, -6, 18, -2		0.53 (0.05)		
<i>FnoGo – ChoGo:</i>				
inferior frontal gyrus, orbital part (47), 36, 20, -16	0.50 (0.08)			-0.63 (0.04)
superior temporal gyrus (22), -50, 0, 0				
lingual gyrus (18), 20, -70, 0		0.55 (0.05)	0.63 (0.06)	0.80 (<0.01)

Table 4

Correlation between ROI modulation and task performance and personality trait measures, female subjects only. The ROI and its coordinates are defined as the activation/deactivation areas in females only, as described in Table 2A. The table lists the correlation coefficients with the p values in the parenthesis.

A. Correlation between ROI modulation and task performance (accuracy and reaction time).			
	Accuracy	Reaction time	
<i>CnoGo activation:</i>			
R. inferior temporal gyrus, 68, -34, 16	0.43 (0.10)	0.55 (0.03)	
<i>CnoGo deactivation:</i>			
Precuneus (31), -6, 58, 26	-0.48 (0.07)		
<i>FnoGo deactivation:</i>			
R. inferior occipital gyrus (18), 32, -88, -6		-0.39 (0.11)	
<i>CnoGo – FnoGo:</i>			
middle temporal gyrus (39), 50, -68, 2		0.46 (0.08)	
<hr/>			
B. Correlation between ROI modulation and personality trait measures.			
	NEO-PI-R		ZKPQ
	impulsivity	excitement-seeking	impulsivity sensation-seeking (ss)
<i>CnoGo deactivation:</i>			
Superior frontal gyrus (10), -6, 58, -6		-0.48 (0.06)	
<i>FnoGo activation:</i>			
L. inferior frontal gyrus orbital part (47), -48, 20, -10	-0.49 (0.06)		0.54 (0.06)
R. Middle frontal gyrus (10), 30, 56, 28			-0.52 (0.08)
Insula, 46, 12, -2			-0.63 (0.02)
Anterior cingulate cortex (32), 4, 42, 20	-0.76 (<0.001)		-0.68 (0.01)
<i>FnoGo – CnoGo:</i>			
orbital surface (47), 52, 30, -6			-0.94 (<0.001)
anterior cingulate cortex (32), 2, 42, 20	-0.94 (<0.001)		-0.62 (0.03)
inferior frontal gyrus, orbital part (47), -50, 22, -10	-0.53 (0.05)	0.52 (0.07)	-0.90 (<0.001)
		0.62 (0.03)	-0.61 (0.04)

Table 5

Correlation between ROI modulation and task performance and personality trait measures for male subjects. The ROIs are defined as those that showed significant sex difference and their coordinates are described in Table 2C.

	Reaction time	NEO-PI-R excitement-seeking
ACC (CX,M-F)	-0.64 (0.02)	0.62 (0.03)
Middle temporal (CX-WX,F-M)	0.66 (0.01)	