2015

Neural systems mediating decision-making and response inhibition for social and nonsocial stimuli in autism

K. M. Shafritz
Northwell Health

J. D. Bregman
Northwell Health

T. Ikuta

P. R. Szeszko
Hofstra Northwell School of Medicine

HHS Public Access

Author manuscript

Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2016 July 03.

Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2015 July 3; 60: 112–120. doi:10.1016/j.pnpbp.2015.03.001.

NEURAL SYSTEMS MEDIATING DECISION-MAKING AND RESPONSE INHIBITION FOR SOCIAL AND NONSOCIAL STIMULI IN AUTISM

Keith M. Shafritz, Ph.D.[a,b,*], **Joel D. Bregman, M.D.**[b,f], **Toshikazu Ikuta, Ph.D.**[c], and **Philip R. Szeszko, Ph.D.**[b,d,e]

[a]Department of Psychology, 135 Hofstra University, Hempstead, NY 11549

[b]Feinstein Institute for Medical Research, North Shore-LIJ Health System, 350 Community Drive, Manhasset, NY 11030

[c]Department of Communication Sciences and Disorders, University of Mississippi, University, MS 38677

[d]Zucker Hillside Hospital, Psychiatry Research, 75-59 263rd Street, Glen Oaks, NY 11004

[e]Hofstra North Shore – LIJ School of Medicine, Hempstead, NY 11549

[f]The Center for Autism, 3905 Ford Road, Philadelphia, PA 19131

Abstract

Autism is marked by impairments in social reciprocity and communication, along with restricted, repetitive and stereotyped behaviors. Prior studies have separately investigated social processing and executive function in autism, but little is known about the brain mechanisms of cognitive control for both emotional and nonemotional stimuli. We used functional magnetic resonance imaging to identify differences in neurocircuitry between individuals with high functioning autism (HFA) and neurotypical controls during two versions of a go/no-go task: emotional (fear and happy faces) and nonemotional (English letters). During the letter task, HFA participants showed hypoactivation in ventral prefrontal cortex. During the emotion task, happy faces elicited activation in ventral striatum, nucleus accumbens and anterior amygdala in neurotypical, but not HFA, participants. Response inhibition for fear faces compared with happy faces recruited occipitotemporal regions in HFA, but not neurotypical, participants. In a direct contrast of emotional no-go and letter no-go blocks, HFA participants showed hyperactivation in extrastriate cortex and fusiform gyrus. Accuracy for emotional no-go trials was negatively correlated with activation in fusiform gyrus in the HFA group. These results indicate that autism is associated

*Address correspondence: keith.shafritz@hofstra.edu, or: Dr. Keith Shafritz, Department of Psychology, 135 Hofstra University, Hempstead, NY 11549. Tel: (516) 463-4856, Fax: (516) 463-6052.

The authors declare no competing financial interests.

with abnormal processing in socioemotional brain networks, and support the theory that autism is marked by a social motivational deficit.

Keywords

Autism Spectrum Disorder; Emotion; Cognition; Executive Function; fMRI

1. Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairments in social reciprocity, interaction and communication, and restricted/repetitive interests and behaviors. A prominent feature of ASD is an inability to implement socially appropriate behaviors or choose the most fitting behavioral response in a given social situation. Such behavioral flexibility requires the identification of facial expressions, eye movements, and body posture, coupled with the cognitive control mechanisms provided by executive functions (EF) such as planning, monitoring, and inhibiting prepotent responses.

Studies indicate altered functioning within brain regions responsible for socioemotional and EF processes in autism (Dichter and Belger, 2007; Dichter et al., 2009; Kana et al., 2007; Kleinhans et al., 2009; Schmitz et al., 2006; Shafritz et al., 2008), but most have investigated social and emotional aspects of human behavior apart from the cognitive control mechanisms necessary to implement appropriate behaviors. Therefore, little is known about the underlying neural processes that bridge cognitive control mechanisms with emotional processing in ASD. It is also unclear whether social impairments in ASD are related to emotion recognition deficits; some studies document impaired emotional recognition (Ashwin et al., 2006a; Pelphrey et al., 2002; Rump et al., 2009), while others show no impairments (Ashwin et al., 2006b; Corbett et al., 2009; Geurts et al., 2009; Monk et al., 2010; Wang et al., 2004). Previously observed deficits in emotional face recognition may be driven primarily by impairments in rapid decision-making with social stimuli, rather than a deficit in emotion recognition, per se (Clark et al., 2008). Prominent theories explaining emotion recognition deficits in autism invoke hypoactivity in fusiform gyrus during face processing tasks (Corbett et al., 2009; Pelphrey et al., 2007; Schultz et al., 2000), but not all evidence supports this notion (Duerden et al., 2013; Hadjikhani et al., 2004; Perlman et al., 2011).

Another proposal suggests that a motivational deficit in which social information is not rewarding may underlie social impairments in ASD (Dawson et al., 2005), but limited evidence supports this hypothesis. There is some indication of diminished neural responses in nucleus accumbens/ventral striatum during the anticipation of social reward (Richey et al., 2014) and during a social reward learning task (Scott-Van Zeeland et al., 2010), and in dorsal striatum during the receipt of social reward (Delmonte et al., 2012). However, other studies have found hypoactivation in these brain regions in ASD during anticipation or receipt of monetary rewards, but not social rewards (Dichter et al., 2012a; Dichter et al., 2012b; Kohls et al., 2013).

The current study sought to address these limitations and contradictory findings. We used functional magnetic resonance imaging (fMRI) to examine whether regional brain activation would differ between ASD and control groups during a letter go/no-go task and an emotional go/no-go task. The emotional go/no-go (Hare et al., 2005; Shafritz et al., 2006) examines rapid decision-making coupled with emotion recognition by requiring participants to quickly respond or inhibit responses to faces of varying emotions. Prior work has demonstrated that dorsal anterior cingulate cortex (ACC) and lateral prefrontal cortex are strongly implicated in nonemotional go/no-go performance, while pregenual ACC is differentially recruited by specific emotions in emotional go/no-go paradigms (Albert et al., 2012; Shafritz et al., 2006). Moreover, relatively intact emotional go/no-go performance has been observed in ASD (Duerden et al., 2013; Geurts et al., 2009), and any observed deficits on this task may be related to the desire to view emotional faces, rather than a deficit in decision-making regarding these faces (Yerys et al., 2013). Further, no studies have used the go/no-go to examine the neural correlates of decision-making in both emotional and nonemotional contexts in autism. Although prior fMRI work (Duerden et al., 2013) has examined response inhibition for social stimuli in autism, this study lacked a nonemotional control condition crucial for distinguishing cognitive control processes mediating response inhibition in social contexts from those involved in generic response inhibition. Therefore, the current study was designed to examine whether previously observed activation differences during emotional go/no-go tasks in ASD are specific to emotional stimuli or reflect deficits in more domain-general response inhibition.

Based on prevailing literature, we hypothesized that (1) during the letter go/no-go, participants with ASD would show decreased activation compared with controls in EF circuitry; (2) during the emotional go conditions, participants with ASD would also show reduced activation compared with controls in amygdala (Ashwin et al., 2007; Monk et al., 2010) for fear stimuli relative to happy stimuli, and in ventral striatum (Hare et al., 2005) for happy stimuli relative to fear stimuli; (3) contrasting fear no-go with happy no-go would yield activation differences in pregenual ACC (Albert et al., 2012; Shafritz et al., 2006); (4) for emotional no-go, participants with ASD would show increased activation in fusiform compared with controls (Duerden et al., 2013).

2. Methods

2.1 Subjects

Participants in the autism group were 20 individuals (17 male, 3 female) with High Functioning Autism (HFA), recruited from the Linder Center for Autism and Developmental Disabilities within the North Shore-LIJ Health System. All participants met DSM-IV criteria for either Autistic Disorder (n=14) or Asperger's Disorder (n=6), established through the Autism Diagnostic Interview-Revised (Lord et al., 1994) and the Autism Diagnostic Observation Schedule-Generic (Lord et al., 2000), administered by an experienced psychiatrist (J.B.). Five participants in this group failed to meet motion criteria for fMRI data analysis (see Functional Image Analysis) and were excluded from the final sample. Therefore, the final HFA sample consisted of 15 individuals (12 male, 3 female; 11 meeting criteria for Autistic Disorder, 4 meeting criteria for Asperger's Disorder; mean age 18.1

years, age range 13–23). Exclusion criteria were presence of co-morbid mood, anxiety, psychotic, or seizure disorders, or Attention-Deficit/Hyperactivity Disorder, and IQ<70. IQ scores were obtained using the Wechsler Abbreviated Scale of Intelligence (WASI). Mean (SD) IQ scores for the autism group were: Full-Scale = 101.5 (18.6), Verbal = 105.7 (18.8), Performance = 103.5 (17.4). Five participants reported no history of medication use. Two reported a history of psychostimulant use, but were free of medication at the time of study. Eight participants were currently using the following medications (numbers in parentheses): citalopram (2); escitalopram (1); alprozolam (1); venlafaxine (1); sertraline (1); aripiprazole (2); clomipramine (1); lithium (1) and guanfacine (1). Based on psychiatric evaluations, symptoms shared with other conditions (such as anxiety or impulsivity) were best attributed to autism rather than independent co-morbid disorders. Hence, medications targeted symptoms related to autism.

Eighteen age- and sex-matched neurotypical control participants (15 male, 3 female) were recruited by advertisement. Three participants in this group failed to meet fMRI motion criteria and were excluded. Therefore, the final control group consisted of 15 individuals (12 male, 3 female; mean age 18.4 years, age range 12–23). All participants in this group were screened through detailed interviews to assure absence of psychiatric, neurological, or developmental disorders. Mean (SD) IQ scores for the control group were: Full-Scale = 115.2 (9.3), Verbal = 118.8 (14.9), Performance = 108.0 (8.1). Full-Scale IQ scores differed between the autism and control groups ($p < .05$), but this difference was driven by a marginal difference in verbal IQ ($p = .05$); there were no between-group differences in performance IQ ($p = .39$). Considering the characteristic impairment in verbal communication among individuals with autism, the difference in verbal IQ was expected.

All participants (and parents or guardians if applicable) received a complete verbal description of the study. This study was approved by the North Shore – LIJ Institutional Review Board and written informed consent was obtained from all participants or parents (with written assent from participants) as appropriate.

2.2 fMRI Task

The task was a block design go/no-go task, using a design similar to our prior work (Shafritz et al., 2006). In the letter version, participants viewed a series of letters and were visually instructed to either respond (by pressing a response button) for all letters that appeared, or respond to all letters except for ‘X’. In the emotional version, participants viewed happy, fearful, or neutral faces and were instructed to either press for all faces, or withhold responses specifically for happy or fearful faces. By including the letter task, we could determine whether any between-group activation differences observed during the emotion task were related specifically to the processing of emotional stimuli, or reflected more domain-general inhibitory processes. Letter stimuli were uppercase consonant English letters in bold Courier New font. Emotional face stimuli were twelve male and twelve female Ekman faces (i.e., happy, fearful, and neutral faces from four male and four female actors) from the Pictures of Facial Affect set (www.paulekman.com). Stimuli were presented using E-Prime v1.1.3 (www.pstnet.com) and reverse-projected onto a screen viewed through a mirror located over the participant’s head.

In the go condition of the letter task, participants viewed a series of 16 letters (not including 'X') and were visually instructed, "Press for all letters," via an instruction screen (3 sec). In the letter no-go condition, participants viewed a series of 16 letters (50% were 'X') and were instructed, "Do not press for 'X'." Figure 1 depicts sample trials from the task.

In the emotion task, participants viewed happy, fearful, or neutral faces and were instructed to either press for all faces, or withhold responses specifically for happy or fearful faces. To determine the distinct neural circuitry engaged by happy and fearful faces, as well as the neural regions responsible for inhibiting responses for happy and fearful faces, the emotion task was divided into several conditions. During happy, fear, or neutral go conditions, 16 faces of one particular emotion were presented, and participants were instructed, "Press for all faces," via an instruction screen (3 sec). In the happy no-go condition, 16 presentations were evenly divided between happy and fearful faces (or happy and neutral faces) and participants were instructed, "Do not press for happy faces." Similarly, during the fear no-go condition, 16 presentations were evenly divided between fearful and happy faces (or fearful and neutral faces) and participants were instructed, "Do not press for fearful faces." (Figure 1). Neutral no-go blocks were not included; participants in pilot testing found it difficult to specifically search for and inhibit responses to neutral faces, perhaps reflecting the ambiguous nature of these faces. However, we kept neutral targets in the paradigm to determine whether inhibition for emotional faces among neutral faces differed from inhibition for a specified emotion among stimuli with a competing emotion.

The task was comprised of ten alternating blocks presented in a pseudorandom order: a letter go block followed by a letter 'X' no-go block, a neutral go block followed by a fear no-go block, a neutral go block followed by a happy no-go block, a fear go block followed by a happy no-go block, and a happy go block followed by a fear no-go block. Each emotional no-go block was always preceded by its corresponding go block to build a tendency to respond to faces of one emotion and then create a response conflict by adding faces of another emotion. For example, when a fear no-go block followed a happy go block, the participant continued to respond to happy faces during the fear no-go block (consistent with the preceding block) and inhibited responses for fear faces.

Blocks were 30 seconds in length, with 16 trials per block. Stimuli were presented for 500ms, followed by a fixation cross for 1000 ms. Each go block consisted of 100% go trials, and each no-go block consisted of 50% go trials and 50% no-go trials randomly presented. This ratio was chosen to be consistent with the pioneering go/no-go block designs used in child and clinical groups (Casey et al., 1997; Vaidya et al., 1998). Each run (6 min 9 sec) consisted of one complete sequence of the task. Data were acquired over 4 runs, with 40 blocks in total and 4 blocks (64 trials) of each task condition. Runs began and ended with 30 second rest blocks consisting of a central fixation cross. Importantly, go/no-go block pairs were pseudorandomly ordered between runs to counterbalance the effects of scanner drift.

2.3 Acquisition of MRI Data

Images were acquired on a 3T GE Signa MRI scanner equipped with an 8-channel phased array coil and gradients for echo-planar blood oxygen level-dependent (BOLD) imaging. T1-weighted anatomical localizer imagers were first collected in the sagittal plane using

conventional parameters, followed by a high-resolution (.94mm × 1.00mm × .94mm) 3-D spoiled gradient recalled (SPGR) sequence collected in the coronal plane to use for co-registration of functional images. $T2^*$-weighted BOLD images were then acquired using the following parameters: 26 axial-oblique slices parallel to the anterior-posterior commissural (AC-PC) line, TR: 1500ms, TE: min full, flip angle: 60°, slice thickness: 5.0mm, in-plane resolution: 3.75mm × 3.75mm, acquisition matrix: 64 × 64 pixels over a field of view of 24cm × 24cm. A total of 246 volumes were acquired in each of 4 functional runs. The first six volumes from each run were discarded to account for initial fluctuation in magnetization.

2.4 Functional Image Analysis

Data analysis for functional images proceeded using a conventional approach for block-design emotional go/no-go tasks (Elliott et al., 2002; Hummer et al., 2013; Shafritz et al., 2006; Wessa et al., 2007). Prior to statistical analysis, images from each run were motion corrected (realigned), co-registered to the SPGR image, normalized to the standard Montreal Neurological Institute (MNI) template with 2 mm^3 voxel size, and Gaussian-filtered (full-width at half-maximum = 6.0 mm) using the SPM8 program (www.fil.ion.ucl.ac.uk/spm). Scans were discarded if movement away from the first collected volume exceeded 3 mm of translational movement in the x, y, or z direction, or 3° of rotation. Statistical parametric maps of BOLD activation were created for each subject meeting motion criteria by estimating signal parameters (β-coefficients) for each of the individual go and no-go conditions using the conventional delayed boxcar function ascribed by SPM8. Baseline fixation periods were not specified in the model to prevent over-parameterization of the task. Individual subject task-contrast maps were then created using t-tests to directly examine signal difference between no-go conditions and their corresponding go conditions (to examine inhibitory processing), happy go and fear go conditions (to examine differences between emotions), and happy no-go and fear no-go conditions (to examine the potential influence of specific emotions on response inhibition). To confirm differences between the three go conditions, one-way ANOVAs compared signal difference between happy go, fear go, and neutral go blocks. To determine brain regions specifically more engaged by emotional go/no-go compared with letter go/no-go, images from the two emotional no-go conditions were combined (Shafritz et al., 2006) and then directly contrasted with images from the letter no-go task.

Group composite contrast maps were created for each comparison by averaging the signal change for each contrast at each voxel and determining the probability that the percent signal change across subjects was different than zero using a t-test at each voxel (second-level random-effects analysis). These contrast maps were created independently for the HFA and control groups. To directly compare activations between the two groups, between-group contrast maps were then created using two-sample t-tests for each task contrast.

Although Lieberman and Cunningham (2009) suggest a threshold of $p<.005$ (uncorrected) with a 10 voxel extent to adequately balance Type I and Type II errors for social and affective designs, we chose to be more conservative in our approach. Therefore, the resulting maps from within-group task contrasts and between-group comparisons were determined by using a threshold of $p<.001$, corrected for multiple comparisons using a

cluster-filter of 10 contiguous voxels (Forman et al., 1995). This threshold is in line with, although not identical to, recent clinical literature using similar task designs (Weathers et al., 2013; Wessa et al., 2007).

3. Results

3.1 Behavioral Performance

Accuracy (percent correct) and reaction time (RT) data for each type of trial during inhibition (no-go) blocks are shown in Table 1. Performance data were not recorded for one control subject due to equipment failure. A 2×5 (Group X Trial Type) repeated-measures Analysis of Variance (ANOVA) compared the accuracies for different types of go trials in inhibition blocks. Results indicated a main effect for Trial Type, $F(4,27) = 8.57$, $p < .001$, but no main effect for diagnostic group, $F(1,27) = 2.13$, nor a Group by Trial Type interaction, $F(4,27) = 1.44$. Because there were no effects of group, data were collapsed across the two diagnostic groups. The main effect for Trial Type was assessed further using post-hoc paired-samples t-tests to compare the accuracy for each type of go trial. Results indicated a higher accuracy for letter go trials compared with fear go, happy go, or neutral go trials ($p < .001$ for all comparisons), and higher accuracy for happy go compared with fear go ($p < .05$). No other significant differences were observed.

A similar repeated-measures ANOVA compared the accuracy for no-go trials. Results indicated a main effect for Trial Type, $F(4,27) = 9.38$, $p < .001$, a marginally significant effect for diagnostic group, $F(1,27) = 3.17$, $p = .086$, and no Group by Trial Type interaction, $F(4,27) = 1.05$. Data from both groups were then collapsed, and post-hoc paired-samples t-tests indicated a higher accuracy for letter ‘X’ no-go trials compared with both fear no-go and happy no-go trials ($p < .005$ for both comparisons), but no statistical differences for accuracy among no-go trials for the two emotions.

A final repeated-measures ANOVA compared reaction times (RT) for go trials within inhibition blocks. Results indicated a main effect for Trial Type, $F(4,27) = 25.52$, $p < .001$, but no main effect for diagnostic group, $F(1,27) = 1.03$, nor a Group by Trial Type interaction, $F(4,27) = 1.64$. Data from both groups were collapsed, and post-hoc paired-samples t-tests indicated faster RT for letter go trials compared with fear go, happy go, or neutral go trials ($p < .001$ for all comparisons), and faster RT for neutral go trials among happy faces compared with neutral go trials among fear faces ($p < .001$).

3.2 Imaging Data

Letter go/no-go—For control participants, within-group task contrast maps of no-go blocks relative to go blocks (see hypothesis 1) revealed activation in bilateral ACC, right DLPFC, right premotor cortex, and bilateral VLPFC extending into the anterior insular cortex (Figure 2A, Table 2). In the HFA group, activations occurred in these regions, with the exception of VLPFC/insula (Figure 2A, Table 3). Direct comparison of activations between the two groups revealed increased activation in right VLPFC/insula in the control group compared with the autism group (Figure 2B, Table 4).

Emotional go/no-go—For both HFA and control participants, within-group task contrast maps comparing emotional no-go conditions with emotional go conditions revealed activation throughout the cortical EF network, including right DLPFC, bilateral ACC and VLPFC/insula, and right intraparietal sulcus (IPS). Tables 2 and 3 provide regions of activation for specific emotional no-go conditions relative to corresponding go conditions.

To examine the neural circuitry engaged by specific emotional facial expression when no executive decision was required (see hypothesis 2), we directly compared activation for the fear go, happy go conditions, and neutral go conditions. Control participants showed increased activation for happy faces compared with fear faces in left lateral PFC, left orbitofrontal cortex, and left ventral striatum, extending into the nucleus accumbens and amygdala (Figure 3A, Table 2), but no increases in activation for fear faces compared with happy faces. By contrast, HFA participants showed no activation differences between go conditions. Direct between-group comparison for happy go vs. fear go confirmed increased activation in the control group in ventral striatum and anterior amygdala (Figure 3B, Table 4).

Finally, to examine the influence of specific emotional expression on the neural circuitry engaged by response inhibition (see hypothesis 3), we directly compared activation between the happy no-go and fear no-go conditions. In the control group, no activation differences were observed. However, the HFA group showed increased activation in pregenual ACC (at the intersection of dorsal and ventral cingulate) when inhibiting responses for happy faces compared with inhibiting for fear faces, and in precuneus/cuneus, fusiform and lingual gyri, superior temporal sulcus, posterior parietal cortex, and amygdala when inhibiting responses for fear faces compared with inhibiting for happy faces (Table 3). Direct between-group comparison for fear no-go vs. happy no go confirmed increased activation in the HFA group in precuneus/cuneus and amygdala (Figure 4A, Table 4). Direct between-group comparison for happy no-go vs. fear no-go revealed a group difference in pregenual cingulate (p=.002) and also in left basal ganglia (Figure 4A, Table 4).

Emotional no-go vs. Letter no-go—For both control and HFA participants, directly contrasting activation between emotional no-go and letter no-go conditions (see hypothesis 4) resulted in activation in ventral temporal and extrastriate cortex, particularly fusiform gyrus, with activations extending ventrally into the cerebellum (Figure 4B, Tables 2 and 3). The extent of activation was greater for HFA participants, and direct between-group comparison revealed a group difference in extrastriate cortex, particularly fusiform gyrus, but at a lower statistical threshold (Figure 4B, Table 4).

3.3 Correlation Between Imaging Data and Task Performance

To determine whether BOLD activations were associated with go/no-go task performance, Pearson correlations assessed degree of association between accuracy for emotional no-go trials and BOLD signal change observed at each voxel in the emotional no-go vs. letter no-go contrast. No reliable correlations were observed in the control group. In the HFA group, a significant and strong positive correlation was observed in dorsal ACC (coordinates of local maximum [10, 38, 28], r = .73). Significant and strong negative correlations were observed

in right fusiform gyrus ([18,−72,−16], r = −.71), right occipitotemporal junction ([36,−78, 20], r = −.80), left lingual gyrus ([−10,−82,−8], r = −.73), and left basal ganglia ([−22, 8,−2], r = −.72). To examine these relationships further, Pearson correlation assessed degree of association between accuracy for each no-go task condition and β-coefficients estimating BOLD signal change for that task condition. No reliable correlations were observed in the control group. In the HFA group, for fear no-go, a significant positive correlation was observed in cuneus ([0,−60, 14], r = .82) and significant negative correlations were observed in fusiform gyrus ([18,−72,−16], r = −.73), bilateral insula/superior temporal cortex ([−44,−2,−10], r = −.77; [44,16,−10], r = −.83; and [46,2,−16], r = −.75), and left VLPFC/ insula ([−38,20,−8], r = −.75).

3.4 Correlation Between Imaging Data and Demographic/Clinical Measures

Adolescence and young adulthood is associated with changes in frontal cortical activation during inhibitory tasks (Shafritz et al., 2006; Tamm et al., 2002). To determine whether age-related maturational processes or IQ differences may have influenced our data, we correlated age and IQ with BOLD data for each task contrast using a whole-brain voxelwise multiple regression for each diagnostic group. No significant correlations were observed in regions activated by the task contrasts, and all reported activations remained after covarying for either age or IQ.

A similar technique correlated BOLD signal change in the autism group with scores on the Qualitative Abnormalities in Reciprocal Social Interaction Domain and the Restricted, Repetitive, and Stereotyped Patterns of Behavior Domain of the ADI-R. No significant correlations were observed in the regions activated by the task contrasts.

4. Discussion

In this study, we determined whether individuals with autism utilized different brain regions compared with typically-developing individuals when completing response inhibition tasks in emotional and nonemotional contexts. Consistent with our first hypothesis, we found that during response inhibition for nonemotional stimuli, participants with autism lacked typical activation observed in lateral inferior frontal cortex and insula. Contrary to predictions, however, we observed no significant differences in DLPFC, ACC, or basal ganglia. Consistent with our second hypothesis, we found that happy faces (relative to fear faces) elicited activation in ventral striatum and nucleus accumbens in the control group, but not the HFA group. Interestingly, we also observed increased activation in anterior amygdala for happy faces relative to fear faces in control, but not HFA, participants. Based on prior evidence, we had expected to find this group difference in the contrast of fear faces relative to happy faces (Ashwin et al., 2007; Monk et al., 2010). In partial agreement with our third hypothesis, we found that response inhibition for happy faces relative to response inhibition for fear faces recruited pregenual ACC in the HFA group, but not the control group. In addition, response inhibition for fear faces relative to response inhibition for happy faces recruited extrastriate cortex and amygdala in the HFA group, but not the control group. Consistent with our fourth hypothesis, we observed greater activation of fusiform gyrus among HFA participants, compared with controls, specifically during emotional no-go conditions. Moreover, emotional no-go task performance among HFA participants was

negatively correlated with activation in fusiform. Overall task performance did not significantly differ between groups. Therefore, between-group activation differences cannot be accounted for simply by performance differences, and these activation differences likely represent underlying neural mechanisms of the disorder itself apart from cognitive performance (Duerden et al., 2013; Elliott et al., 2002; Hummer et al., 2013; Wang et al., 2004). Activations specific to the HFA group may reflect compensatory brain mechanisms allowing for successful completion of the task.

The current study is unique in a variety of ways. By combining emotional face stimuli with an EF task, we were able to directly model within a single experimental paradigm socio-emotional impairments and executive impairments observed in individuals with autism. This novel design represents a significant advance over prior fMRI work that relied on the use of nonemotional face stimuli during response inhibition (Dichter et al., 2009), emotion- and face-matching paradigms that did not directly investigate response inhibition (Corbett et al., 2009), or emotional go/no-go tasks without a control task (Duerden et al., 2013). Similarly, our design models cognitive and emotional processes apart from those required by social reward tasks (Delmonte et al., 2012; Dichter et al., 2012b; Kohls et al., 2013; Rademacher et al., 2010; Richey et al., 2014; Scott-Van Zeeland et al., 2010; Stavropoulos and Carver, 2014), in that our task requires decisions specifically about emotional faces, rather than an emotional face being the outcome of a response. Although these prior studies provide a solid foundation in the study of cognitive control and social deficits in autism, their conclusions may be limited because they did not directly investigate inhibitory control for emotional stimuli compared with nonemotional stimuli. Therefore, the control conditions employed in the current study help to resolve ambiguous findings from prior literature by allowing for the direct comparison of neural recruitment under several experimental conditions. Moreover, an important strength of our task design is that participants must look at the emotional faces in order to maintain good task performance, thereby ensuring that all participants examined the faces closely enough to determine the emotion conveyed by the face.

Within this context, perhaps our most intriguing finding was the lack of ventral striatal/accumbens activation in the HFA group for happy faces relative to fear faces. Heightened ventral striatal activation for happy faces relative to fear faces in typically-developing individuals has been observed during a go/no-go task (Hare et al., 2005). Likewise, activation of ventral striatum has also been observed during anticipation of happy faces as a social reward in a speeded response task (Rademacher et al., 2010). These regions, strongly linked to reward and motivation, have also been found to be hypoactive in participants with autism during monetary incentive tasks (Dichter et al., 2012a; Dichter et al., 2012b; Kohls et al., 2013; Scott-Van Zeeland et al., 2010) and occasionally during social incentive tasks (Richey et al., 2014; Scott-Van Zeeland et al., 2010). Consistent findings for monetary reward, but not social reward, have suggested that autism may involve dysregulation in motivational processes in general. It has been difficult to draw firm conclusions regarding the influence of motivational processes on social and emotional function in autism. Our current finding of selective activation of ventral striatum and accumbens when viewing and responding to happy faces in controls, but not in participants with autism, further indicates that autism is characterized by a deficit in social motivation. It is conceivable that typically-developing individuals appreciate in a hedonic way viewing happy faces when also viewing

fearful faces (Hare et al., 2005), but individuals with autism lack this enjoyment. This hypothesis is consistent with the proposal that social impairments in autism may be caused by a motivational deficit by which social information is not rewarding (Dawson et al., 2005; Sepeta et al., 2012). Future studies requiring individuals with ASD to rate their enjoyment of viewing happy faces while inside the scanner would lend further support to this developing theory.

Another important finding in the current study was hyperactivation of fusiform gyrus in HFA participants when comparing response inhibition for emotional stimuli with inhibition for letter stimuli. Because the fusiform may play a prominent role in the evaluation of faces (Kanwisher et al., 1997), this region has come under intense scrutiny in ASD research. Earlier findings indicated that ASD is marked by a lack of activation in this region when viewing emotional face stimuli (Schultz et al., 2000). However, more recent studies using social decision-making tasks suggest that fusiform face area functions normally in ASD (Hadjikhani et al., 2004; Perlman et al., 2011), is hyper-responsive in ASD (Duerden et al., 2013), or is under-responsive only for novel faces (Pierce and Redcay, 2008). We suggest that these prior inconsistent results are due to differences in task demands. Our current results are consistent with the recent finding that fusiform is hyper-responsive in ASD individuals when deciding whether to respond depending on the emotion depicted by facial stimuli (Duerden et al., 2013). Hyperactivation of fusiform observed in the current study may reflect increased neural processing needed to perform this task well despite its inherent difficulty for some ASD individuals. Our finding that task performance was negatively correlated with activation in this region strongly supports this idea, as HFA subjects who performed poorly on the task recruited fusiform more than those who performed well. To our knowledge, this finding is the first indication that fusiform activation may be proportional to how well individuals with ASD process and respond to emotional face stimuli. This correlation may help to explain previously conflicting results observed at the group level and suggests that within-group performance must always be taken into account when examining putative activation differences.

When evaluating hypothesis 3, we observed that HFA subjects selectively recruited amygdala and extrastriate cortex when inhibiting responses for fear faces relative to inhibiting for happy faces, and in pregenual ACC when inhibiting responses for happy faces relative to inhibiting for fear faces. In these comparisons, motor components of the task are identical, and activation differences can be attributed to the emotion to which the subject responded (Shafritz et al., 2006). Alternatively, the contrast of the two emotional no-go conditions may reflect cognitive set shifting due to the necessity to remap stimulus-response rules. Regardless, it is clear that the emotion task was more cognitively demanding than the letter task, and group differences in neural activation during emotional no-go conditions may be due in part to this greater demand. Further, although there is no agreement as to whether a deficit in identifying emotional facial expressions is a universal feature of autism, research suggests that fear may be particularly difficult for individuals with autism to recognize (Ashwin et al., 2007; Ashwin et al., 2006a; Pelphrey et al., 2002). The selective recruitment of amygdala and pregenual ACC by the HFA group in these task comparisons might reflect the difficulty inherent in this task and the additional cognitive effort required to process fearful faces among competing happy faces while maintaining good task performance.

Indeed, the lack of performance differences between the HFA and neurotypical groups suggests that HFA participants were able to discriminate between happy and fearful faces, and that recognition of these basic emotions appears intact in HFA.

The letter task was included in our design to determine differences between neural circuitry engaged by emotionally-guided response inhibition and domain-general response inhibition. During this task, we observed reduced activation in inferior frontal/insular regions in the HFA group compared with the control group. These regions of VLPFC have been strongly implicated in attention (Gitelman et al., 1999; LaBar et al., 1999) and response inhibition (Casey et al., 2001; Rubia et al., 2001; Shafritz et al., 2005). It is conceivable that lack of inferior frontal/insular activation in the HFA group reflects a more efficient neural processing of response inhibition, as performance was equivalent with controls. However, hypoactivation of VLPFC has been previously related to EF deficits in autism (Dichter and Belger, 2007; Kana et al., 2007; Shafritz et al., 2008). The current findings are in line with these prior results, and provide additional corroborative evidence for hypoactivation during response inhibition even with equivalent performance.

It is interesting to note that we did not observe increased activation in lateral PFC for emotional no-go relative to letter no-go, and that group differences were observed in this region only during the letter task. We suggest that prefrontal differences observed only during the letter task may reflect deficits in neural processing in ASD for domain-general cognitive control, while differences observed in posterior brain regions (such as fusiform) may reflect deficits specifically in cognitive control related to social stimuli. Unexpectedly, we did not observe group differences during the letter task in other EF processing regions, such as DLPFC or dorsal ACC. It is plausible that because our task was relatively easy for both groups to complete, the task did not engage the EF network heavily enough to observe potential activation differences in areas other than VLPFC.

Results of the current study are limited by a number of factors. First, the block design limits our ability to examine the neural correlates of specific cognitive components of response inhibition, such as perceiving the stimulus, making a decision, and executing that decision. However, use of an event-related design to isolate these components would make our task exceedingly long and not suitable for a clinical population. Further, a temporally-spaced event-related go/no-go task would not incorporate the continuous and prepotent responding desired here. For these reasons, recent clinical studies using the emotional go/no-go paradigm have used block designs (Duerden et al., 2013; Hummer et al., 2013; Wessa et al., 2007). Importantly, however, the block design allowed us to expeditiously examine response inhibition in a tightly controlled manner, even if we could not disentangle its constituent cognitive components.

In this regard, we also acknowledge the limitation of not using a stringent $p<.05$, FWE-corrected threshold; however, our use of a threshold of $p<.001$ with a 10 voxel extent was chosen apriori. This rationale was based on prior evidence and theoretical viewpoints (Lieberman and Cunningham, 2009; Weathers et al., 2013) and prior work using a block design decision-making task with socioemotional stimuli and strict sensorimotor controls. Such tasks do not generally produce data that are as robust as data from simple event-related

perceptual or motor tasks. Therefore, only moderate effect sizes and more variable subject-to-subject results are expected for designs such as ours, and many of the designs in the realm of affective neuroscience generally do not survive the stringent statistical thresholds used in simple perceptual or motor tasks (Lieberman and Cunningham, 2009).

Another possible limitation is potential differences in task requirements between the emotional and nonemotional versions of our go/no-go task. As noted above, the contrast of the two emotional no-go conditions may, in part, reflect cognitive set shifting due to the necessity to remap stimulus-response rules. Because we only have one nonemotional no-go condition, this potential cognitive shift is not required by the letter task. Combining the emotional no-go conditions into a single contrast to compare with letter no-go ameliorates this potential confound. However, we do note that it may be difficult to reliably interpret activation differences for the comparison of fear no-go and happy no-go due to the inability to disentangle set shifting from emotional valence. We also acknowledge the significant difference in full-scale IQ between the two groups. However, IQ was not correlated with the activations observed in either group; all activations remained after controlling for IQ scores, indicating that IQ differences did not significantly impact our results.

5. Conclusion

In summary, our findings demonstrate differential neural processing between autism and neurotypical individuals during response inhibition tasks with both socio-emotional and nonsocial stimuli. These neural processing differences were apparent despite equivalent task performance between the two groups, and thus, likely reflect specific neural dysfunction in HFA. These findings provide novel insight into the underlying brain mechanisms of decision-making in autism, particularly decisions related to emotional aspects of human behavior.

Acknowledgments

We thank Linda Spritzer, Melissa Buchman, Rachel Ginsberg, and Elizabeth Mansdorf for help with subject recruitment, cognitive test administration, and data analysis; Dr. Peter Kingsley and John Ferrannini for technical assistance with MRI data collection; Blair Shevlin and Cori Fisher for help with paradigm development and fMRI data analysis. This study was funded by National Institutes of Health Grant M01RR018535 and grants from Hofstra University.

References

Albert J, Lopez-Martin S, Tapia M, Montoya D, Carretie L. The role of the anterior cingulate cortex in emotional response inhibition. Hum Brain Mapp. 2012; 33:2147–2160. [PubMed: 21901794]

Ashwin C, Baron-Cohen S, Wheelwright S, O'Riordan M, Bullmore ET. Differential activation of the amygdala and the 'social brain' during fearful face-processing in Asperger Syndrome. Neuropsychologia. 2007; 45:2–14. [PubMed: 16806312]

Ashwin C, Chapman E, Colle L, Baron-Cohen S. Impaired recognition of negative basic emotions in autism: a test of the amygdala theory. Soc Neurosci. 2006a; 1:349–363. [PubMed: 18633799]

Ashwin C, Wheelwright S, Baron-Cohen S. Finding a face in the crowd: testing the anger superiority effect in Asperger Syndrome. Brain Cogn. 2006b; 61:78–95. [PubMed: 16455174]

Casey BJ, Forman SD, Franzen P, Berkowitz A, Braver TS, Nystrom LE, Thomas KM, Noll DC. Sensitivity of prefrontal cortex to changes in target probability: a functional MRI study. Hum Brain Mapp. 2001; 13:26–33. [PubMed: 11284044]

Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LN, Giedd JN, Castellanos FX, Haxby JV, Noll DC, Cohen JD, Forman SD, Dahl RE, Rapoport JL. A developmental functional MRI study of prefrontal activation during performance of a go-nogo task. J Cogn Neurosci. 1997; 9:835–847. [PubMed: 23964603]

Clark TF, Winkielman P, McIntosh DN. Autism and the extraction of emotion from briefly presented facial expressions: stumbling at the first step of empathy. Emotion. 2008; 8:803–809. [PubMed: 19102591]

Corbett BA, Carmean V, Ravizza S, Wendelken C, Henry ML, Carter C, Rivera SM. A functional and structural study of emotion and face processing in children with autism. Psychiatry Res. 2009; 173:196–205. [PubMed: 19665877]

Dawson G, Webb SJ, McPartland J. Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. Dev Neuropsychol. 2005; 27:403–424. [PubMed: 15843104]

Delmonte S, Balsters JH, McGrath J, Fitzgerald J, Brennan S, Fagan AJ, Gallagher L. Social and monetary reward processing in autism spectrum disorders. Mol Autism. 2012; 3:7. [PubMed: 23014171]

Dichter GS, Belger A. Social stimuli interfere with cognitive control in autism. Neuroimage. 2007; 35:1219–1230. [PubMed: 17321151]

Dichter GS, Felder JN, Bodfish JW. Autism is characterized by dorsal anterior cingulate hyperactivation during social target detection. Soc Cogn Affect Neurosci. 2009; 4:215–226. [PubMed: 19574440]

Dichter GS, Felder JN, Green SR, Rittenberg AM, Sasson NJ, Bodfish JW. Reward circuitry function in autism spectrum disorders. Soc Cogn Affect Neurosci. 2012a; 7:160–172. [PubMed: 21148176]

Dichter GS, Richey JA, Rittenberg AM, Sabatino A, Bodfish JW. Reward circuitry function in autism during face anticipation and outcomes. J Autism Dev Disord. 2012b; 42:147–160. [PubMed: 22187105]

Duerden EG, Taylor MJ, Soorya LV, Wang T, Fan J, Anagnostou E. Neural correlates of inhibition of socially relevant stimuli in adults with autism spectrum disorder. Brain Res. 2013; 1533:80–90. [PubMed: 23962468]

Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ. The neural basis of mood-congruent processing biases in depression. Arch Gen Psychiatry. 2002; 59:597–604. [PubMed: 12090812]

Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med. 1995; 33:636–647. [PubMed: 7596267]

Geurts HM, Begeer S, Stockmann L. Brief report: inhibitory control of socially relevant stimuli in children with high functioning autism. J Autism Dev Disord. 2009; 39:1603–1607. [PubMed: 19543821]

Gitelman DR, Nobre AC, Parrish TB, LaBar KS, Kim YH, Meyer JR, Mesulam M. A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. Brain. 1999; 122 (Pt 6):1093–1106. [PubMed: 10356062]

Hadjikhani N, Joseph RM, Snyder J, Chabris CF, Clark J, Steele S, McGrath L, Vangel M, Aharon I, Feczko E, Harris GJ, Tager-Flusberg H. Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. Neuroimage. 2004; 22:1141–1150. [PubMed: 15219586]

Hare TA, Tottenham N, Davidson MC, Glover GH, Casey BJ. Contributions of amygdala and striatal activity in emotion regulation. Biol Psychiatry. 2005; 57:624–632. [PubMed: 15780849]

Hummer TA, Hulvershorn LA, Karne HS, Gunn AD, Wang Y, Anand A. Emotional response inhibition in bipolar disorder: a functional magnetic resonance imaging study of trait- and state-related abnormalities. Biol Psychiatry. 2013; 73:136–143. [PubMed: 22871393]

Kana RK, Keller TA, Minshew NJ, Just MA. Inhibitory control in high-functioning autism: decreased activation and underconnectivity in inhibition networks. Biol Psychiatry. 2007; 62:198–206. [PubMed: 17137558]

Kanwisher N, McDermott J, Chun MM. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci. 1997; 17:4302–4311. [PubMed: 9151747]

Kleinhans NM, Johnson LC, Richards T, Mahurin R, Greenson J, Dawson G, Aylward E. Reduced neural habituation in the amygdala and social impairments in autism spectrum disorders. Am J Psychiatry. 2009; 166:467–475. [PubMed: 19223437]

Kohls G, Schulte-Ruther M, Nehrkorn B, Muller K, Fink GR, Kamp-Becker I, Herpertz-Dahlmann B, Schultz RT, Konrad K. Reward system dysfunction in autism spectrum disorders. Soc Cogn Affect Neurosci. 2013; 8:565–572. [PubMed: 22419119]

LaBar KS, Gitelman DR, Parrish TB, Mesulam M. Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. Neuroimage. 1999; 10:695–704. [PubMed: 10600415]

Lieberman MD, Cunningham WA. Type I and Type II error concerns in fMRI research: re-balancing the scale. Soc Cogn Affect Neurosci. 2009; 4:423–428. [PubMed: 20035017]

Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, Pickles A, Rutter M. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord. 2000; 30:205–223. [PubMed: 11055457]

Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord. 1994; 24:659–685. [PubMed: 7814313]

Monk CS, Weng SJ, Wiggins JL, Kurapati N, Louro HM, Carrasco M, Maslowsky J, Risi S, Lord C. Neural circuitry of emotional face processing in autism spectrum disorders. J Psychiatry Neurosci. 2010; 35:105–114. [PubMed: 20184808]

Pelphrey KA, Morris JP, McCarthy G, Labar KS. Perception of dynamic changes in facial affect and identity in autism. Soc Cogn Affect Neurosci. 2007; 2:140–149. [PubMed: 18174910]

Pelphrey KA, Sasson NJ, Reznick JS, Paul G, Goldman BD, Piven J. Visual scanning of faces in autism. J Autism Dev Disord. 2002; 32:249–261. [PubMed: 12199131]

Perlman SB, Hudac CM, Pegors T, Minshew NJ, Pelphrey KA. Experimental manipulation of face-evoked activity in the fusiform gyrus of individuals with autism. Soc Neurosci. 2011; 6:22–30. [PubMed: 20446172]

Pierce K, Redcay E. Fusiform function in children with an autism spectrum disorder is a matter of "who". Biol Psychiatry. 2008; 64:552–560. [PubMed: 18621359]

Rademacher L, Krach S, Kohls G, Irmak A, Grunder G, Spreckelmeyer KN. Dissociation of neural networks for anticipation and consumption of monetary and social rewards. Neuroimage. 2010; 49:3276–3285. [PubMed: 19913621]

Richey JA, Rittenberg A, Hughes L, Damiano CR, Sabatino A, Miller S, Hanna E, Bodfish JW, Dichter GS. Common and distinct neural features of social and non-social reward processing in autism and social anxiety disorder. Soc Cogn Affect Neurosci. 2014; 9:367–377. [PubMed: 23223206]

Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, Simmons A, Williams SC, Giampietro V, Andrew CM, Taylor E. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. Neuroimage. 2001; 13:250–261. [PubMed: 11162266]

Rump KM, Giovannelli JL, Minshew NJ, Strauss MS. The development of emotion recognition in individuals with autism. Child Dev. 2009; 80:1434–1447. [PubMed: 19765010]

Schmitz N, Rubia K, Daly E, Smith A, Williams S, Murphy DG. Neural correlates of executive function in autistic spectrum disorders. Biol Psychiatry. 2006; 59:7–16. [PubMed: 16140278]

Schultz RT, Gauthier I, Klin A, Fulbright RK, Anderson AW, Volkmar F, Skudlarski P, Lacadie C, Cohen DJ, Gore JC. Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. Arch Gen Psychiatry. 2000; 57:331–340. [PubMed: 10768694]

Scott-Van Zeeland AA, Dapretto M, Ghahremani DG, Poldrack RA, Bookheimer SY. Reward processing in autism. Autism Res. 2010; 3:53–67. [PubMed: 20437601]

Sepeta L, Tsuchiya N, Davies MS, Sigman M, Bookheimer SY, Dapretto M. Abnormal social reward processing in autism as indexed by pupillary responses to happy faces. J Neurodev Disord. 2012; 4:17. [PubMed: 22958650]

Shafritz KM, Collins SH, Blumberg HP. The interaction of emotional and cognitive neural systems in emotionally guided response inhibition. Neuroimage. 2006; 31:468–475. [PubMed: 16480897]

Shafritz KM, Dichter GS, Baranek GT, Belger A. The neural circuitry mediating shifts in behavioral response and cognitive set in autism. Biol Psychiatry. 2008; 63:974–980. [PubMed: 17916328]

Shafritz KM, Kartheiser P, Belger A. Dissociation of neural systems mediating shifts in behavioral response and cognitive set. Neuroimage. 2005; 25:600–606. [PubMed: 15784439]

Stavropoulos KK, Carver LJ. Reward anticipation and processing of social versus nonsocial stimuli in children with and without autism spectrum disorders. J Child Psychol Psychiatry. 2014; 55:1398–1408. [PubMed: 24890037]

Tamm L, Menon V, Reiss AL. Maturation of brain function associated with response inhibition. J Am Acad Child Adolesc Psychiatry. 2002; 41:1231–1238. [PubMed: 12364845]

Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, Gabrieli JD. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. Proc Natl Acad Sci U S A. 1998; 95:14494–14499. [PubMed: 9826728]

Wang AT, Dapretto M, Hariri AR, Sigman M, Bookheimer SY. Neural correlates of facial affect processing in children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2004; 43:481–490. [PubMed: 15187809]

Weathers J, Brotman MA, Deveney CM, Kim P, Zarate C Jr, Fromm S, Pine D, Leibenluft E. A developmental study on the neural circuitry mediating response flexibility in bipolar disorder. Psychiatry Res. 2013; 214:56–65. [PubMed: 23958598]

Wessa M, Houenou J, Paillere-Martinot ML, Berthoz S, Artiges E, Leboyer M, Martinot JL. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. Am J Psychiatry. 2007; 164:638–646. [PubMed: 17403978]

Yerys BE, Kenworthy L, Jankowski KF, Strang J, Wallace GL. Separate components of emotional go/no-go performance relate to autism versus attention symptoms in children with autism. Neuropsychology. 2013; 27:537–545. [PubMed: 23937480]

Highlights

- We modeled decision-making in socio-emotional and nonsocial contexts in autism
- Autism group lacked activation in ventral striatum and accumbens for happy faces
- Autism group showed hypoactivation in frontal cortex for nonsocial response inhibition
- Autism group showed hyperactivation in fusiform gyrus for social response inhibition
- Findings indicate aberrant neural processing in autism during social decision-making

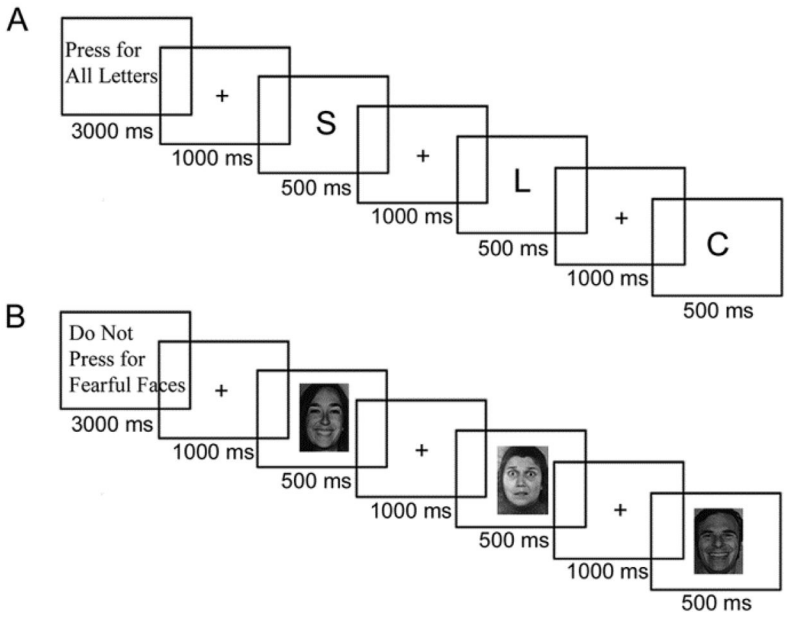

Figure 1.

Sample task designs for (A) a go block during the letter task, and (B) a fear no-go block during the emotion task. In the letter task, subjects viewed a series of letters and pressed a response button for each letter presented (go blocks) or for every letter, except 'X' (no-go blocks). In the emotion task, subjects viewed happy, fearful, and neutral faces and pressed a response button for all faces (go blocks) or specifically for happy or fear faces (no-go blocks).

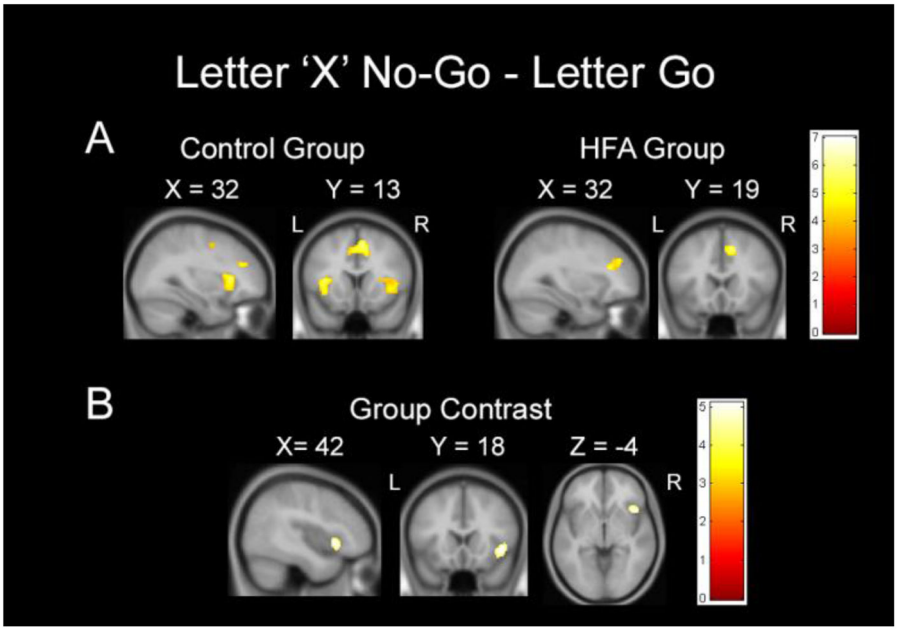

Figure 2.

(A) Within-group task contrast maps depicting brain activation for the letter 'X' no-go condition relative to the letter go condition. Maps show areas of significant signal increase during the no-go condition relative to the go condition exceeding p=.001, corrected with a cluster filter of 10 contiguous voxels. Numerical values next to the color bars indicate the t-value for each color. Positions (in mm) in Montreal Neurological Institute (MNI) coordinate space are shown above each slice. (B) Between-group contrast maps showing regions of increased activation for the control group compared with the High Functioning Autism (HFA) group during the letter 'X' no-go task.

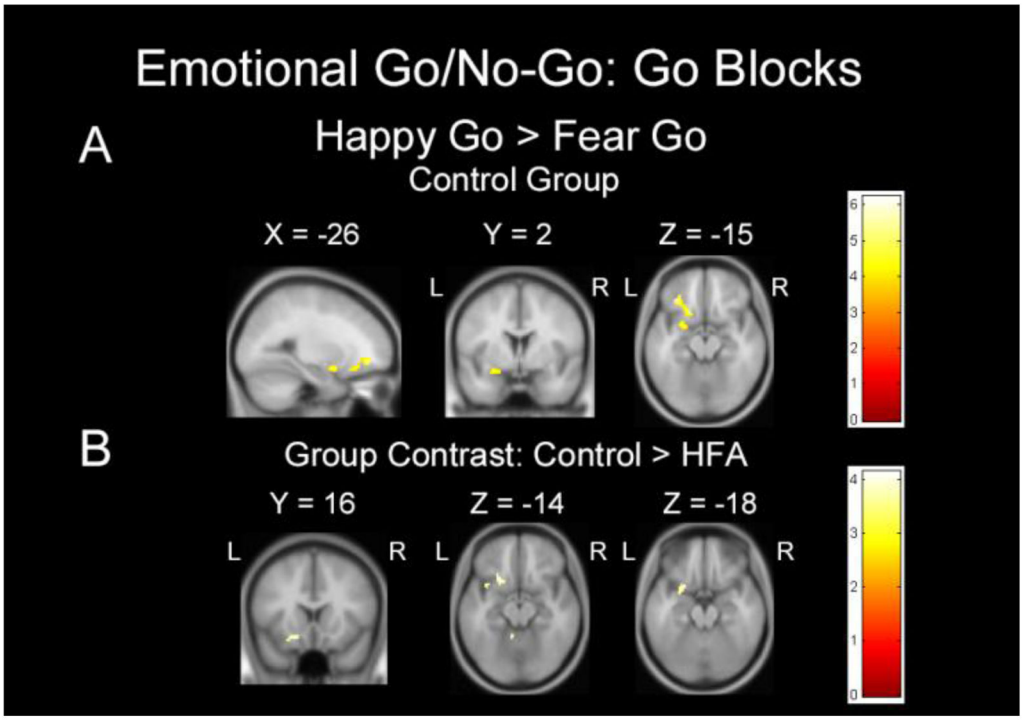

Figure 3.

(A) Within-group task contrast maps for the emotional go conditions. Maps show areas of significant signal increase during the happy go condition relative to the fear go condition for the control group ($p<.001$, corrected with a cluster filter of 10 contiguous voxels). Numerical values and positions as in Figure 2. (B) Between-group contrast maps showing regions of increased activation for the control group compared with the HFA group during the happy go condition relative to the fear go condition.

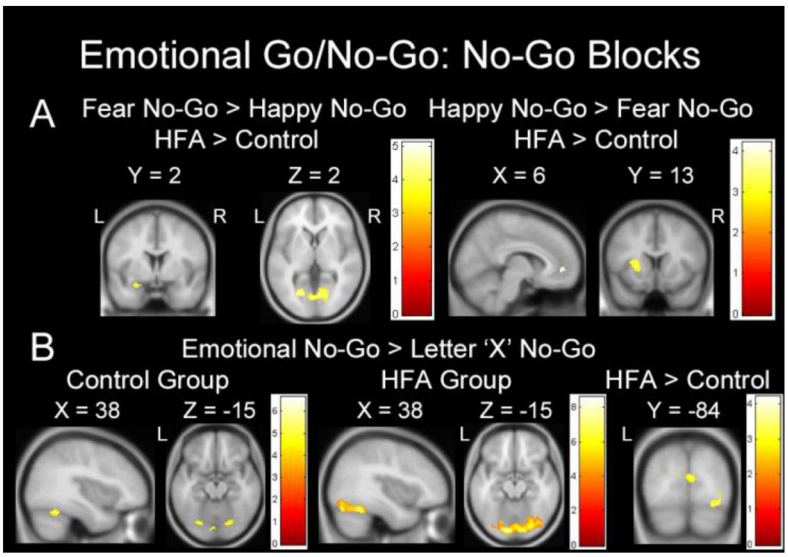

Figure 4.

(A) Between-group contrast maps comparing the emotional no-go conditions. Maps on the left depict brain regions significantly more activated by the HFA group compared with controls for the contrast of fear no-go vs. happy no-go. Maps on the right depict brain regions significantly more activated by the HFA group compared with controls for the contrast of happy no-go vs. fear no-go. Numerical values and positions as in Figure 2. (B) Within-group and between-group contrast maps showing regions of significant signal increase for the emotional no-go conditions compared with the nonemotional (letter 'X') no-go condition.

Table 1

Performance Data for No-Go Blocks.

Task Condition	Control Group M(SD)	Autism Group M(SD)
Accuracy (% Correct)		
Letter Go	100.00(0)	99.40(2.32)
Letter No-Go	93.21(7.37)	89.00(16.16)
Fear Go	93.21(8.05)	92.40(7.68)
Fear No-Go among Neutral	91.93(6.62)	81.93(12.64)
Fear No-Go among Happy	87.29(8.97)	77.00(19.56)
Happy Go	96.14(3.42)	95.00(6.45)
Happy No-Go among Neutral	93.43(7.40)	85.53(16.70)
Happy No-Go among Fear	85.93(8.96)	80.07(16.83)
Neutral Go among Fear	97.86(2.18)	91.73(7.75)
Neutral Go among Happy	93.14(7.89)	92.13(6.14)
Reaction Time (ms)		
Letter Go	430.6(99.3)	407.7(47.8)
Fear Go	507.7(94.4)	488.1(87.2)
Happy Go	520.2(100.5)	463.3(69.3)
Neutral Go among Fear	504.7(95.2)	479.0(75.0)
Neutral Go among Happy	475.6(81.4)	454.7(66.1)

Table 2

Regions of Activation in the Control Group, p<.001 cluster-filtered to 10 contiguous voxels.

			MNI Coordinates		
Location of Activation Cluster	**Brodmann's Area**	**Tmax**	**x**	**y**	**z**
'X' No-Go – Letter Go					
Dorsolateral Prefrontal Cortex (DLPFC)	9/46	4.79	32	38	24
Anterior Cingulate Cortex (ACC)	32	6.53	8	18	42
Ventrolateral PFC (VLPFC), right	45	5.54	32	24	6
VLPFC/Insula, left	45	7.02	−38	10	8
Premotor Cortex (PMC), right	6	4.63	40	6	34
Happy No-Go – Neutral Go					
ACC	32	5.13	10	14	44
PMC, right	6	5.01	32	2	48
DLPFC, right	9/46	4.25	36	34	24
VLPFC/Insula, right	45	4.14	32	26	4
VLPFC/Insula, left	45	5.25	−34	16	10
Intraparietal Sulcus (IPS), right	40	4.52	38	−50	38
Fear No-Go – Neutral Go					
ACC/Dorsal Frontal Gyrus	6/32	4.59	2	22	46
PMC, right	6	4.85	44	8	42
VLPFC/Insula, right	45	6.02	42	26	4
VLPFC/Insula, left	45	4.95	−38	18	4
IPS, right	7/40	4.43	34	−58	44
Happy No-Go – Fear Go					
ACC, right	32	6.34	10	16	42
ACC, left	32	5.37	−10	20	36
DLPFC, right	46	4.63	42	36	18
PMC, right	6	5.63	32	2	50
Insula, right	NA	4.96	38	18	8
Insula, left	NA	6.43	−36	16	8
IPS, right	40	7.08	34	−60	40

Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2016 July 03.

Location of Activation Cluster	Brodmann's Area	Tmax	MNI Coordinates x	y	z
Thalamus, right	NA	4.52	12	−8	8
Fear No-Go – Happy Go					
ACC/Superior Frontal Gyrus	6/32	4.81	4	18	46
VLPFC/Insula, right	45	4.29	38	24	2
Happy Go – Fear Go					
Lateral Orbitofrontal Cortex (OFC), left	47	6.23	−30	42	−8
OFC, left	47	4.97	−42	44	−8
Ventral Caudate/Accumbens, left	NA	4.90	−18	20	−14
Anterior Amygdala, left	NA	4.58	−26	4	−14
Lateral PFC, left	10	5.35	−34	52	12
Emotional No-Go – Letter No-Go					
Fusiform Gyrus/Cerebellum, left	37	6.64	−36	−54	−20
Fusiform Gyrus/Cerebellum, right	37	5.25	36	−56	−22
Fusiform Gyrus, left	18	5.54	−22	−76	−18
Fusiform Gyrus, right	18	4.97	20	−74	−16

Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2016 July 03.

Table 3

Regions of Activation in the Autism Group, p<.001 cluster-filtered to 10 contiguous voxels.

			MNI Coordinates		
Location of Activation Cluster	**Brodmann's Area**	**Tmax**	**x**	**y**	**z**
'X' No-Go – Letter Go					
Dorsolateral Prefrontal Cortex (DLPFC)	9/46	5.79	30	32	20
Anterior Cingulate Cortex (ACC)	32	5.95	12	18	46
Inferior Frontal Gyrus	6/44	6.20	48	8	28
Happy No-Go – Neutral Go					
ACC/Dorsal Frontal Gyrus	6/32	7.40	12	14	52
Inferior Frontal Gyrus	6/44	7.27	46	10	16
Ventrolateral PFC (VLPFC)/Insula	47	5.99	42	22	−4
Intraparietal Sulcus (IPS)	7/40	5.75	34	−58	40
Fusiform Gyrus, right	37	4.82	46	−60	−18
Fusiform Gyrus, left	18/19	4.97	−38	−72	−18
Fear No-Go – Neutral Go					
Inferior Frontal Gyrus	44	7.90	38	18	16
DLPFC, right	9/46	6.03	38	36	22
VLPFC/Insula, right	47	7.29	34	24	0
VLPFC/Insula, left	47	7.46	−30	24	2
ACC, right	32	6.83	8	22	44
ACC, left	32	7.51	−4	22	44
IPS, right	7/40	6.55	40	−56	42
Fusiform Gyrus, right	19/37	7.26	38	−50	−16
Fusiform Gyrus, left	19/37	6.68	−42	−52	−16
Happy No-Go – Fear Go					
ACC, Superior Frontal Gyrus	8/32	7.42	6	20	46
DLPFC, right	9/46	6.33	42	34	30
Premotor Cortex, left	6	8.35	−42	4	32
VLPFC/Insula, right	45	6.80	32	24	4
VLPFC/Insula, left	45	6.40	−30	20	8

			MNI Coordinates		
Location of Activation Cluster	**Brodmann's Area**	**Tmax**	**x**	**y**	**z**
Inferior Parietal Lobule, right	40	6.86	42	−58	44
Fusiform Gyrus, right	19/37	7.06	40	−68	−10
Fear No-Go – Happy Go					
ACC, Superior Frontal Gyrus	6/32	5.96	6	18	46
VLPFC/Insula, right	45	4.79	32	26	2
IPS, right	7/40	4.18	34	−58	48
Fusiform Gyrus, right	37	4.64	42	−58	−24
Happy No-Go – Fear No-Go					
Pregenual Cingulate Cortex	24/32	4.58	2	40	8
Pregenual Cingulate Cortex	24/32	4.26	2	48	0
Fear No-Go – Happy No-Go					
Precuneus, right	23	4.51	16	−54	14
Cuneus, left	31	5.17	−14	−64	10
Fusiform/Lingual Gyrus, right	18/19	4.26	18	−70	−4
Fusiform/Lingual Gyrus, left	18/19	4.51	−14	−74	−8
Superior Temporal Sulcus, left	21/22	5.04	−46	6	−18
Posterior Parietal Cortex, left	7	4.56	−36	−74	40
Amygdala, left	NA	3.79	−24	2	−20
Emotional No-Go – Letter No-Go					
Fusiform/Lingual Gyrus, left	18/19	8.59	−14	−86	−14
Fusiform Gyrus/Cerebellum, right	18/19/37	7.74	34	−58	−20
Fusiform Gyrus, right	18	6.50	14	−80	−20
Lingual Gyrus, right	18	5.99	6	−74	6

Table 4

Regions of Activation Difference between Autism and Control Groups, p<.001 cluster-filtered to 10 contiguous voxels.

			MNI Coordinates		
Location of Activation Cluster	**Brodmann's Area**	**Tmax**	**x**	**y**	**z**
'X' No-Go – Letter Go (Control>Autism)					
Ventral Prefrontal Cortex/Insula, right	45/47	4.46	44	18	−2
Happy Go – Fear Go (Control>Autism)					
Ventral Caudate/Accumbens, left	NA	4.14	−20	18	−14
Anterior Amygdala, left	NA	3.89	−24	10	−18
Fear No-Go – Happy No-Go (Aut>Control)					
Lingual Gyrus/Cuneus, left	18/31	5.10	−20	−68	4
Lingual Gyrus/Cuneus, right	18/31	4.48	14	−70	4
Amygdala, left	NA	4.07	−26	2	−18
Happy No-Go – Fear No-Go (Aut>Control)					
Pregenual Cingulate Cortex	24/32	3.18, p=.002	2	46	0
Basal Ganglia, left	NA	3.36	−24	14	4
Emotional No-Go – Letter 'X' No-Go					
Fusiform Gyrus, right	18	2.89, p=.004	30	−84	−16
Extrastriate Cortex, Cuneus	18	2.89, p=.004	4	−84	10

Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2016 July 03.