Functional MRI of Emotional Face Processing in Schizophrenia and the Social Cognition Psychometric Correlates

Sascha Qian

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FUNCTIONAL MRI OF EMOTIONAL FACE PROCESSING IN SCHIZOPHRENIA AND THE SOCIAL COGNITION PSYCHOMETRIC CORRELATES

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Sascha Qian

2012
FUNCTIONAL MRI OF EMOTIONAL FACE PROCESSING IN SCHIZOPHRENIA AND THE SOCIAL COGNITION PSYCHOMETRIC CORRELATES

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This is the first report on the correlation of social cognitive psychometrics to functional MRI regional brain activation in amygdala, fusiform gyrus, and insular cortex during passive viewing of happy, sad, and neutral faces from Gur’s University of Pennsylvania series in patients with schizophrenia. Both patients and controls showed activation of bilateral amygdala, fusiform, and insular cortex compared to baseline. ROI analysis of activation maps from 14 patients and 11 matched healthy controls revealed significant differences across emotional faces in bilateral fusiform gyrus and insula, though not in amygdala. Healthy controls showed significantly higher activation in the insular cortex ($p < 0.05$) and in the fusiform gyrus ($p < 0.05$) during processing of sad compared to happy faces while patients with schizophrenia showed no significance difference. Both patients ($p < 0.05$) and controls ($p < 0.05$) had higher activation in the fusiform gyrus during processing of sad compared to neutral faces. Patients with schizophrenia scored significantly lower on Social Skills Performance Assessment, Hinting Task, Rosenberg Self-Esteem Intake, NEO Personality Profile agreeableness scale and significant higher on 6/7 BORRTI dimensions and NEO neuroticism scale. Factor analyses reduced to the psychometrics to 4 dimensions—social output, general social, cognitive and affective empathy, and personal distress. Of those, social output corresponded the most to patients’ insular cortex activation during sad ($r=-0.815, p<0.001$) and neutral ($r=-0.556, p<0.05$) facial processing and to patients’ insular ($r=0.815, p<0.001$) and fusiform ($r=0.631, p<0.05$) activation difference between happy and sad facial processing. Cognitive & affective empathy correlated to insular cortex activation difference between viewing happy and neutral faces ($r=0.675, p<0.05$) and personal distress corresponded to fusiform activation difference between sad and neutral ($r=0.565, p<0.05$).

Results suggest that Social Output, having strong neural correlates, may be a useful dimension in understanding social cognition.
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Introduction

Emotional face processing in Schizophrenia

Core features of schizophrenia include deficits in not only neurocognition but also in social functioning. Impairment of social functioning in patients with schizophrenia can present in early childhood, years before the first episode of psychosis, and remain through the whole course of the illness, even after treatment with antipsychotic medication (Addington et al 2000, Davidson et al 1999). Impaired social functioning is an important predictor of clinical outcome (Perlick et al 1992). While much of past research efforts has been focused on understanding how traditional neurocognitive skills (i.e. memory, attention) contribute to social behavior, there is now a burgeoning interest in specific aspects of cognition that underlie social functioning. In particular, “emotional face processing”, or the ability to perceive the emotion disposition of others through processing faces, is a highly salient topic of discussion—it is a fundamental component of social cognition since it is a likely an initial step in the social communication (Edwards et al 2002, Morrison RL 1988).

Faces convey displays of emotion and impart meaningful information to the external world. Successfully reading others’ facial expressions permits one to detect another’ emotional state and pick up cues on how to respond in the subsequent social interactions (Frank MG et al 2001). Among healthy subjects, basic emotions interpreted from facial expressions (i.e fear, disgust, anger, happiness, sadness) are universal in their performance and perception (Adolphs et al 2002). Among patients with schizophrenia, misidentification of basic emotions may occur as early as less than 50 ms within exposure to stimuli, suggesting that deficits of emotional face processing are part of unconscious preprocessing (Tsoi et al 2008, Gordon et al 1992).

Yet, intact emotional face processing is crucial to participating in social environments and navigating interactions with others (Damsio 2000). Patients with schizophrenia who cannot adequately recognize emotional expressions are less likely to maintain friendships or jobs (Green MF et al 2000, Spiegel DE et al 1962). They also have worse clinical treatment outcomes
Despite consistent reporting of deficits in emotional face processing in schizophrenia, the debate lingers as to whether the impairments are due to general difficulty in the processing of facial stimuli, performance, or a specific difficulty in recognizing emotion (Johnston PJ et al 2006, Bryson G et al 1997). It is thought that a significant component of the clinical impairment can be attributed to limitations of processing basic visual information and detecting nonemotional aspects of the facial stimuli (Lee J et al 2007, Chen Y et al 2009, Chen Y et al 2008, Butler et al 2008, Noroton et al 2009). By asking participants to view faces and to judge the emotion as well as other variables (i.e. age, gender), researchers found that patients were significantly more impaired on emotion discrimination tasks than on other visual detection tasks; thus, there is still a component that is not determined solely by processing of basic visual and facial information (Schneider et al 2006, Tsoi et al 2008).

Patients with schizophrenia have also been observed to avoid attending to telling parts of the face such as the eyes and mouth; during visual tracking tasks, they have been observed to devote less time fixating on the eyes and mouth (Loughland et al 2002). Their visual scanning paths are described as “restricted,” “saccadic,” and “short” gazes to the non-eye and non-mouth regions of the face. In contrast, healthy controls rely on staring at the eyes to discriminate fear from other expressions and at the eyes and mouth to distinguish fear from other emotions (Adolphs R 2008, Smith ML 2005). Since patients with schizophrenia avoid the eyes, Kohler et al found that as expected, they were more impaired in discriminating emotions compared to healthy controls and most impaired in discriminating recognizing fear compared to other emotions (Kohler et al 2003). Even after reducing the difficulty of the emotion discrimination task by raising the intensity of the emotion stimuli, Kohler et al found that patients with schizophrenia were found to be significantly more impaired than healthy controls.

Interestingly, patients with schizophrenia tend to stand further away from emotional faces compared to healthy controls, even if it’s a positive emotion such as happiness (Mandal et al, 1998).
Thus, it has been proposed that patients with schizophrenia may have a negative emotive response to emotional face stimuli. They could find gazing at faces, in particular eyes, particularly stressful. This consideration is consistent with significant amygdala activation in response to facial stimuli in previous studies.

**Neural Correlates of Emotional face processing**

Since emotional face processing plays a major role in social functioning, affective neuroscientists over the recent decades have striven to understand more about the neural mechanisms that support face emotional processing. Functional brain imaging techniques such as fMRI, have been favored as informative and powerful tools in understanding the neural substrates of emotional processing.


One region of interest is the fusiform gyrus, for it shows specific activation to faces and has been linked to facial recognition (Chao et al 1999, Puce et al 1996). Lesions in the lateral fusiform gyrus can lead to an inability to recognize the identity of a face, a disorder also known as prosopagnosia (Philips ML et al 2003). Lateral fusiform gyrus tends to be more activated during tasks focused on identity, processing the non-changeable aspects of the face (Haxby et al 2000). Reduced activation in fusiform gyrus is associated with deficits in emotional face
processing in subjects at risk of psychosis (Seiferth et al 2009), younger patients (Seiferth et al 2008), and adult patients (Quintana J 2003). While there are some studies that show that patients with schizophrenia have normal activation in the fusiform gyrus during performance of a task using facial stimuli (Yoon JH et al 2006, Onitsuka T et al 2006), it should be countered that patients seem to have significant structural abnormalities of the fusiform gyrus compared to healthy controls. Specifically, patients’ fusiform show smaller volume of gray matter on the left fusiform gyrus compared to healthy controls (McDonald et al 2000 and Paillere-Martinot 2001).

Another region of great interest is the amygdala for it modulates the fusiform gyrus in relation to the emotional content of faces and identifies the emotional significance of the stimuli (Rotshtein P et al 2001). The amygdala is activated when subjects are gazing at the eye region of fearful faces (Adams RB et al 2003, Whalen PJ et al 200, Morris JS et al 2002). Lesions in amygdala may result in decrease gaze to the eye region and impairment in recognizing expressions of fear more so than other emotions (Adophs et al 2005, Spezio ML et al 2007, Calder AJ et al 1996). Neuroimaging studies have demonstrated abnormalities in the amygdala in patients with schizophrenia during emotional face processing (Habel et al 2004, Hempel et al 2003, Kosaka et al 2002, Schneider et al 1998). Hall et al established that increase in amygdala activity during processing of neutral faces relative to baseline was as much as the increase when viewing fearful faces, signifying the apparent deficit in amygdala activation may be explained by increase in activation to neutral face relative to baseline rather than decrease in activation to fearful face (Hall J et al 2008). One potential confounding is the extent to which activity in amygdala reflects the patients’ increased anxiogenic response to face stimuli. The other confounding is whether the environment whether being in a MRI scanner increases the patients’ baseline amygdala BOLD response more than in healthy controls. Gur et al reported that patients displayed robust bilateral amygdala while failing to recognize fear—thus, increased amygdalar
activity may be impairing task performance in people with schizophrenia (Gur et al 2007). When processing other facial expressions, patients’ extent of activation in the amygdala was reduced compared to healthy controls’ (Li H et al 2010, Schneider et al 1998). The amygdala in patients with schizophrenia appears to be smaller than healthy controls; most recent studies have confirmed a smaller bilateral volume (Wright et al 2000).

Compared to the involvement of amygdala and fusiform gyrus, the role of insula cortex in schizophrenia has been less heavily investigated in the context of emotional face processing. The insula cortex is a cortical structure uniquely involved in the awareness of one’s own internal emotional and physical state, through multiple connections to the other regions of the cortex and the limbic system (Damasio et al 2003, Critchley et al 2004); it receives facial visual information through the inferioral temporal gyrus (Mesulam & Mufson 1982). It has been proposed that based on the insular connections and functions, abnormal processing in this region would likely disrupt the evaluation of emotional stimuli and self (Wylie et al 2010). Emotional stimuli that most engage the insula are of the negative type—anger, fear, and especially disgust; likewise, individuals with lesions to the insula have difficulty recognizing negative facial expressions, especially disgust (Adolphs et al 2000, Calder et al 2000, Adolphs et al 2003).

The same negative emotions of sadness, fear, and disgust are the expressions that patients with schizophrenia have the most challenge in identifying. Patients with schizophrenia have been shown to have abnormal brain activations in response to emotional faces compared to healthy controls—they have decreased hemodynamic response to faces of disgust (Philips et al 1999) and hypo-activation during processing faces of sadness (Seiferth et al 2009) and potentially during faces of fear (Michalopoulou et al 2008). Patients also have bilateral decreased gray matter in the insula (Ellison-Wright et al 2008, Saze et al 2007) and reduced insular cortical thickness (Roiz-Santianez et al 2010).
In conclusion, patients with schizophrenia appear to have abnormal activation in response to various emotional face stimuli across the fusiform gyrus, amygdala, and insular cortex—these regions are also shown to be smaller in volume with structural abnormalities. Individuals from neurological studies with more isolated lesions in fusiform gyrus, amygdala, and insular cortex have similar functional deficits to patients with schizophrenia in recognizing emotional faces, suggesting that abnormalities in these regions make significant contributions to their social cognitive impairment.

Psychometric testing

Though functional MRI is useful for understanding the association between impairment in function and regional activation during a variety of tasks, social cognition is a broad construct and requires tests that have higher ecological validity and ease of administration. Significant scientific effort has been directed towards capturing the relevant features of social functioning in schizophrenia through psychometric testing. Widely used psychometrics in this specific context are designed to measure affect recognition, Theory of Mind, social attribution, personality empathy, object relations, and reality testing. Most of these measures hone in on the ability to recognize or discriminate emotions from photographs or videos, such as Bell-Lysaker Emotion Recognition Task (BLERT) and Revised Eyes Test (Bell et al 1997, Baron-Cohen S et al 2001). Others measures require the participant on role play such as Social Skills Performance Assessment (Patterson et al 2001); oral vignettes to gauge primarily intention inference such as Hinting Task (Greig et al 2004); written questionnaires such as Bell Object Relations & Reality Testing Inventory (BORRTI) (Bell 1995), Interpersonal Reactivity Index (IRI) (Davis 1980), Rosenberg Self-Esteem Intake (Rosenberg 1965), and NEO-Personality Inventory (Costa & McCrae 1989, 1992).

Many of these social cognitive measures have been criticized for focusing too narrowly
on a defined social cognitive process (Green et al 2008). Another important concern is that performance on these tests depends on verbal ability and is limited by the constricted, artificial nature of the tasks (Klin et al 2000). In response, an novel measure, involving a silent cartoon animation of geometric shapes enacting a pure social drama called Social Attribution Test – Multiple Choice (SAT-MC) was adapted from autism research for patients with schizophrenia (Bell et al 2010). Significantly higher portion of patients with schizophrenia compared to healthy community sample was found to have SAT-MC scores in the impairment range.

In 2004, funded by National Institute on Mental Health, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) study was started as an interdisciplinary collaboration to improve treatment of cognitive deficits in schizophrenia (Green and Nuechterlein 2004). It was decided that the first project of MATRICS was to develop a reliable neurocognitive battery to assess social cognition more comprehensively and reliably. The approved final product, MATRICS Consensus Cognitive Battery (MCCB) recommended the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) as the only measure for the domain for social cognition (Nuechterlein et al 2008).

However recently, Mancuso et al suggested 3 more dimensions of social cognition based on a factor analyses—the 4 measures were named hostile attributional style, lower level social cue detection, and higher-level inferential and regulatory processes (Mancuso et al 2011). Hostile attribution style was significantly correlated with functional outcomes (functional capacity and real-world social and work function) while lower-level social cue detection was correlated with clinical symptoms (positive, depression-anxiety, agitation). This study was enlightening in showing that instead of relying MSCEIT as a sole measure of social cognition, there are multiple dimensions that can be separated and investigated as alternatives.
Design of the Experiment

Conceptually speaking, studies involving functional MRI of facial emotional processing are geared towards processes on the scale of milliseconds (within an exposure to a face) while studies involving social cognitive psychometrics are geared towards participants in a constructed “real-world” scenario, a “world” in which they are given ample time to think and deliberate. The ultimate objective of both methods is to probe deeper into the mechanisms of social cognition. Thus, while it is important to know whether results from neuroimaging and neurocognitive psychometrics will ultimately correspond with clinical outcomes, it is also important to determine whether the two methodologies yield results that correlate.

This is the first study to correlate functional MRI of facial emotional processing in patients with schizophrenia with their scoring on social cognitive psychometrics. It would be informative to know which of these widely used psychometrics, however narrowly constructed on an artificial scenario, are meaningful predictors of regional activation patterns; likewise, it would be helpful to know which combination of activation task and region of interest have significant correspondence with the more ecologically meaningful measures of social cognition.

To determine which psychometrics were useful for schizophrenia research, we compared scores from an urban community mental health center (CMHC) with those of a matched community-dwelling sample. To examine the effect of disease (schizophrenia versus healthy control) and the effect of processing emotional face stimuli (happy vs sad vs neutral), we compared fMRI results from the same patient and control subjects across activation tasks and across 3 regions of interest (ROIs). Finally, we determined the psychometrics’ convergent validity with regional brain activation.

The activation tasks selected were passive viewing of faces from Gur’s University of Pennsylvania photographic series, a well-validated set of images conveying basic emotions (Gur
RC et al 2002). Although Ekman’s series has been used widely since 1976, Gur’s series was selected for its high technical quality and the wider ethnic diversity and age range of the faces (Ekman 1976). This study focused on processing of happy, sad, and neutral faces. Unlike the emotions of fear and disgust which are best conveyed through the quick changeable parts of the face such as the raising of eyebrows or the crumpling or the expansion around the mouth, the emotions of happy, sad, and neutral are more static and can be discriminated adequately from stills. The psychometrics selected were a sample of the most established social cognition measures that focused on a diversity of aspects—personality, empathy, object relations, reality testing, intention inference, self-esteem.
Purpose & Hypothesis

Since fMRI is a major tool in the identification of neuropathology associated with different behavioral manifestations of schizophrenia, we proposed a fMRI comparison of regional brain activations in clinically stable outpatients with schizophrenia and appropriately matched healthy control subjects during simulated presentations of affective faces. We will also compare the subjects’ results on various established social cognitive psychometrics that assess emotion recognition, social skills performance, object relations, reality testing, theory of mind, empathy, self-esteem, and personality. Finally, we will evaluate whether there are significant associations between brain activations and scoring on social cognitive psychometrics.

We hypothesize that:

A. Patients will show lower than normal activations of insular cortex, fusiform gyrus, and amygdala after being presented with both happy and sad emotion-evoking photographs of human faces.

B. Patients will appear more like healthy subjects after being presented with emotionally neutral faces than after being presented with emotion-evoking faces.

C. Patients will show exhibit lower scores on psychometrics related to performance assessment of social skills, which includes Social Skills Performance Assessment (SSPA) and Hinting Task.

D. Patients will score higher on alienation, insecure attachment, egocentricity, and social incompetence scales; however, given only clinically stable patients were selected (i.e. no current active psychosis), they will score only marginally higher on reality distortion, uncertainty of perception, hallucinations & delusions scales on Bell Object Relations & Reality Testing (BORRTI).

E. Patients will score lower on Bell-Lysaker Emotion Recognition Task (BLERT) which determines a person’s ability to discriminate between affective states given visual cues; similarly, patients will score lower on Social Attribution Task-Multiple Choice version (SAT-MC) which determines a person’s ability to read an abstracted social scene involving geometrical shapes.

Patients will score lower on Eyes Test, which assesses for theory of mind.
F. Patients will score lower on Rosenberg Self-Esteem Intake, a self-reported measure of self-esteem and will have a significantly different factor profile on the NEO Personality Inventory, scoring most likely higher on neuroticism and lower on extroversion, openness to experience, agreeableness, and conscientious.

G. Of the psychometrics included in this project, the ones that are most likely to have significant associations with brain activations will include BLERT, SAT-MC, as well as Eyes Test as these involve emotion discrimination based on visual cues.
Methods

Of note, the participants were selected by the Wexler lab. The scanning tasks, image acquisition, and psychometric testing were directed by the post-docs of the Wexler lab and conducted as part of a larger study. The author conducted the image processing, statistical analysis, and data interpretations, with supportive feedback from the lab.

Participants

We studied 21 medicated, clinically stable outpatients with SCID-DSM-IV-R diagnoses of schizophrenia or schizoaffective disorder without history of neurological illness, active substance abuse or non-psychiatric medications with CNS effects, and 15 healthy controls who were screened by SCID and matched to patients in gender, age, and parental education (see Table 1). All participants were fluent in English and right handed. Diagnostic interviews and symptoms assessments were done by the head of schizophrenia treatment program in the outpatient division at Connecticut Mental Health Center (CMHC). All participants answered a series of intake questions, including ones focused on how many people they socialize with on a regular basis. All subjects gave written informed consent, and the protocol was approved by the Institutional Review Board of Yale University.

Scanning Tasks

A. Cognitive Testing

All subjects were imaged on two occasions. While viewing the photographs, subjects were cued to recall the pre-learned sequence of 5 numbers every 30 seconds by a yellow circle that appears on the emotion-inducing film. A “blank” tape with a constant gray background with the yellow circle appearing every 30 seconds were presented before the other tapes in order to
re-familiarize subjects with the sequence and procedure, and to provide data on activations associated with the task alone. Subjects were reminded of the sequence before each of the videotapes began.

B. Activation Tasks

At the start of each session, subjects were presented with photographs of facial displays of emotion from Gur’s University of Pennsylvania series and asked to indicate by button push whether each face is of a man or a woman (Gur RE et al 2002). Faces were presented in blocks of either happy, sad, or neutral faces, with an equal number of gray screen baseline periods with a fixation cross in the center. Each block lasted 20 seconds and included five faces in pseudorandom order each presented for 2.5 seconds with 1.5 seconds between faces (see Figure 1). There were two 4-minute runs of this task, yielding 78 images for each of the four conditions (TR 1.5 seconds, see below). This task served two purposes. First, images from all faces were contrasted with images from the gray screen blocks in order to identify the fusiform face area, insula area, and area of amygdalar responses to faces in each subject individually. These were used as individualized ROIs in analyses of activation response to the videotapes. Secondly, brain responses to the different facial affect types were compared in second exploratory comparisons of patients and controls.

Image Acquisition

Imaging was performed at 3 Tesla on a Siemens Trio scanner with high performance gradients (max. gradient strength 40mT/m, 200mT/m/s rise time). Subjects were secured in the head-coil with foam and tape to minimize head movement. Subjects’ arms were at their sides, supported by
foam padding. Studies begun with a T1-weighted sagittal scout scan (spin echo, TE/TR=6.83/20ms, 256x240 matrix, 2 averages, FOV=24cm, 4mm skip 0.8mm) from which the anterior commissure (ac) and posterior commissure (pc) were identified. Twenty-seven T1-weighted, spin echo, axial-oblique slices, parallel to the ac-pc line with the 10th slice centered on the ac-pc line, were then acquired (T1 weighted spin echo, TE/TR 2.47/300ms, 256x256x2nex, FOV=22cm, 4.5mm skip 0, Series 2). The images obtained in Series 2 served as the anatomic images for functional overlay, and these images were registered to the 3D MR volume acquisition acquired at the end of the session. In Series 3 the BOLD gradient echo imaging sequences for recording the blood oxygenation changes were then defined to cover the exact same slice locations as defined in Series 2 using a gradient echo, echo planar imaging (EPI) sequence (FAT/TE/TR = 80/25/150ms, FOV=22cm, matrix 64x64, bandwidth 2520Hz/pix with 6 warm-up pulses. During Series 3, subjects did emotional faces gender identification task, with 2 runs each lasting 4 minutes. At the end of the fMRI study, a 3D volume scan was obtained (MP-RAGE, 256x256x176, FOV=22cm, 1 mm slice thickness, FA/TE/TR/TI=7 deg/3.34/2530/1100ms, bw=180HZ) onto which the fMRI data was registered.

**Data Processing**

The time sequence data for all tasks were motion corrected using SPM5. Individual subject data were analyzed using a General Linear Model (GLM) on each voxel in the entire brain volume with regressors specific for each task (http://bioimagesuite.org). For all the emotional faces tasks, there were one regressor for all face blocks relative to all gray fixation blocks and regressors for each of the happy, sad, and neutral face blocks relate to the gray fixation screen blocks. The resulting functional images for each task were spatially smoothed with a 6mm Gaussian kernel over a two voxel radius to account for variations in the location of activation across subjects. The output maps were normalized beta-maps in the acquired space (3.44mm x 3.44mm x 4.5mm). Three registrations were calculated in Yale Bioimage Suite software package using the intensity-
only component of the method reported by Papademetris et al 2004 to take these data into a common reference space (Duncan et al 2004; Papademetris et al 2004; Papademetris et al 2006). The first registration performed a linear registration between the individual subject raw function image stripped of the skull and that registration between the individual subject raw functional image stripped of the skull and that subject’s 2D anatomical image. The 2D anatomical image was then linearly registered to the individual’s 2D anatomical image. The 3D differed from the 2D in that it has 1x1x1 mm resolution whereas the 2D z-dimension is set by slice-thickness and its x-y dimension were set by voxel size. Finally, a non-linear registration was computed between the individual 3D anatomical image and a reference 3D image. The reference brain used by the Colin27 Brain (Holmes et al, 1998) which was in Montreal Neurological Institute (MNI) space (Evans et al, 1993) as was commonly applied to SPM and other software packages. All three registrations were applied sequentially to the individual normalized beta-maps to bring all data into the common reference space.

**Psychometric Testing**

Psychologists and/or master’s level researchers administered social cognitive assessments. Symptom assessment and social functioning measures were performed by Ph.D. level psychologists trained to high levels of inter-rater agreement. Testing was typically completed over 2 sessions, with breaks as need to reduce fatigue and maintain alertness.

A. SSPA (Social Skills Performance Assessment)

In SSPA, subjects participated in two 3-min role representing social problem situations (Patterson et al 2001). Scenes acted out between an interviewer and participant were audio taped for subsequent scoring. First, a 1-minute interaction served as a practice scene in which
the subject makes plans to get together with a friend (interviewer). In a subsequent 3-minute interaction, the subject played the role of a tenant meeting a new neighbor (interviewer). The objective was to greet the new neighbor in a friendly and informative manner. In the last 3-minute interaction, the subject played the role of a tenant calling the landlord (interviewer) regarding a leak that has gone unrepaired after a previous complaint. The objective was to have the landlord attend to the leak immediately. The interviewer’s role was to reciprocate the conversation initiated by the participant using prescribed prompts as required. Prompts were provided when the participant did not speak for 10 s, and included, “I'm new to the area. Tell me about the neighborhood” and “Have you lived here long?”

Each scene was replayed from tape and scored on a graduated scale by interviewers who were “blind” to the psychiatric ratings, evaluating interest/disinterest, fluency, clarity, focus, affect, grooming, overall conversation, social appropriateness, persistence, overall argument, and negotiation ability.

B. BORRTI (Bell Object Relations & Reality Testing Inventory)

Patients answered a self-report measure with 90 true/false items assessing 4 dimensions of object relations and 3 dimensions of reality testing (Bell 1995). BORRTI was developed initially for schizophrenia research and has been found to have strong psychometric properties in a wide variety of applications and to have cross-cultural validity (Li et al 2008). The Egocentricity scale, in particular, has been linked with measures of social functioning (Bell et al 2009). Examples of items included: I believe a good mother should always please her children (true); people are never honest with each other (true); and others frequently try to humiliate me (true). T-scores were used in this analysis.
C. Bell-Lysaker Emotion Recognition Task (BLERT)

Patients were tested through an affect recognition task consisting of 21 short video clips in which an actor performs 1 of 3 dialogues while portraying 7 different emotions that color the monologue (Bell et al 1997). The subject chose from a list the option that best reflects the affective quality portrayed. For example, monologue 1 was: “I just received my job rating from my supervisor. He called me into his office and gave me a rating of adequate. He told me that I haven’t made any serious mistakes lately.”

After each vignette, the tape was paused, and subject made his or her selection. The test generated several measures including number of correct responses. 21-19 is normal, 18-15 is mild impairment, 14-11 is moderate impairment, 10-7 is moderately severe, 6-0 is severe.
Total correct score was used in this study.

D. Hinting Task.

Patients were tested on a Theory of Mind measure, devised to test the ability of subjects to infer the real intentions behind indirect speech utterances, consisting of 10 brief scenarios of an interaction between 2 people (Greig et al 2004, Corcoran 1995). One of the characters dropped an obvious hint (eg, “Jane, I’d love to wear that blue shirt, but it’s very wrinkled”). The subjects were asked what was meant. An appropriate response was given a score of 2 and then the next story was read. If, however, the subject failed to give the correct response by, for example, simply paraphrasing the ‘hint’ and thus using no inferential skills, more was added to the story in the shape of an even more obvious hint. The subject was then asked again what the character wants to do. If a correct response is delivered, the subject was given as score of one; if not, the
subject received a score of 0. All items on the task read aloud. To take account of the poor prose recall of patients with schizophrenia, the stories were repeated for those who requested that it be so.

E. (Revised) Eyes Test.

Patients were tested on another Theory of Mind measure (Baron-Cohen S et al 2001). Subject were presented with a series of 36 photographs of the eye-region of the face of different actors and actresses and asked to choose which of the four words best describes what the person in the photograph is thinking or feeling.

F. SAT (Social Attribution Task- Multiple Choice version)

SAT was originally developed by Klin (Klin 2000, Klin et al 2006) and used by Bell and colleagues (Bell et al 2010) for schizophrenia research. Patients watched a 64-second animation created by Heider and Simmel (Heider & Simmel 1944) in which geometric shapes enact a social drama. The animation was shown twice and then short segments were presented followed by multiple-choice questions about the actions depicted. In all, 19 questions were asked with 4 possible responses to each. For example, after being shown a short segment, the respondent was asked, “What is the little triangle trying to do?” and given these choices: “(1) It wants to help the little circle. (2) It wants to help the big triangle. (3) It wants to play with the little circle and with the big triangle. (4) It wants to lock the door.” It was scored for total number correct.
G. IRI (Interpersonal Reactivity Index)

Based on the premise that empathy consists of separate but related concepts, IRI was developed as a self-reported measure of dispositional empathy with four 7-item subscales (Perspective Taking, Empathic Concern, Personal Distress, Fantasy). Subjects were asked to circle 1-5 on Likert scale (Davis 1980).

H. Rosenberg Self-Esteem Intake

On a ten item questionnaire assessing self-esteem, subjects circled 1-5 on Likert scale. The total score was reported. (Rosenberg 1965).

I. NEO Personality Inventory

NEO PI-Revised was devised as a 240 item measure of the Five Factor Model- Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness to Experience. Each factor dimension has 6 dimension (Costa & McCrae 1989, 1992).

Statistical Analysis

Statistical analyses were carried using SPSS (SPSS 15.0 Command Syntax Reference 2006) and SPM5 (Wellcome Dept. of Cognitive Neurology 2003). Aggregate images were generated for the control as well as patient group for all emotions; aggregate images were also generated for control and patient groups for the combination of happy and sad in comparison to neutral. Contrast images were generated for each participant for the contrasts of interest (happy > neutral, sad > neutral), representing the pair-wise comparison of parameter estimates for the
condition.

Differences between any of the two groups were examined using two sample t tests. The threshold for all statistical maps at p < 0.05 and clusters large than or equal to 30 voxels were reported. Region of interest (ROI) analysis was conducted for three regions—bilateral amygdala, fusiform, and insula—using a mask derived from the automated anatomical labeling atlas in MNI space, so that measures of regional activation for each emotion condition could be used for statistical analyses in SPSS. The regions were selected based on examination of individual activation maps.

Brain activation for each ROI (insula, amygdala, and fusiform face areas) between normal subjects and patient groups for all emotion conditions (happy, sad, neutral) were compared using a two-way repeated measure analysis of variance (ANOVA). For ROIs that yielded statistical significant different brain activations, post-hoc pair-wise comparisons were conducted to determine the quadratic effects of emotion. Nonparametric methods (Kendall’s tau b and Spearman’s Rho) were used to determine the significance of correlations between regional brain activations for each emotion condition and the behavioral scores on the various social cognitive measures.

Finally, since there were numerous psychometrics in this study and the variations of some measures could be explained by variations of one or fewer measures, factor analyses was performed to reduce the number of variables to a lower number of less correlated factors: Factor A. Social Output Factor (consisting of BORRTI egocentricity and alienation scales, SSPA total score, MSCEIT), Factor B1 General Social Cognitive (consisting of Hinting Task total score, SAT-MC, BLERT), Factor B2 Cognitive and Affective Empathy (Interpersonal Reactivity Index IRI- Empathic Concern, Fantasy, and Perspective Taking), Factor B3 Personal Distress (IRI – Personal Distress).
Results

Demographics & Behavioral Results

Demographic and behavioral results were compiled into Table 1. The main sample (N = 25) was composed of predominantly male (64% in patients and controls) adults (mean age=43.8, SD=9.7). The patients were mostly chronically ill (mean age of onset=25.0, SD=7.2) with diagnosis of either paranoid schizophrenia (64%) or schizoaffective disorder (36%). Most of the patients were on an atypical (57.1%), a conventional (21.4%), or a combination of atypical and conventional antipsychotic regimen (14.3%). Patients and healthy controls did not differ significantly in number of full-time jobs held; however, patients had significantly less years of education (mean=13.1 vs 15.5) and less socialization with community member. According to a self-report assessment, patients had poorer quality of life compared to healthy controls (mean score=61.7 vs 106.7, p<0.05).

Table 1 also showed the descriptive statistics of social cognitive measures that were entered into the subsequent principal components analysis. Patients scored consistently less on Social Skills Performance Assessment (SSPA), Hinting Task, Rosenberg Self-Esteem Intake, Interpersonal Reactivity Index (IRI) Perspective Taking, and Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) compared to healthy controls; they also scored higher on 6/7 of the following Bell Object Relations & Reality Testing Inventory (BORRTI): alienation, insecure attachment, egocentricity, social incompetence, reality distortion, hallucinations and delusions.

Imaging Results

Comparisons between patients with schizophrenia and healthy controls

In aggregate images combining 3 emotion conditions (happy, sad, neutral), healthy controls and patients with schizophrenia did not differ significantly in brain activations (see
Figure 2). Adjusting cluster voxel size from 30 to 0 with threshold maintained at $p < 0.05$, the contrast map between healthy controls and patients, as depicted by the last row of Figure 1, still did not yield any significant clusters (not pictured, similar to Figure 2). Because potential regions of interest may not be picked up due to statistical thresholds, we also wanted to do a careful visual comparison of the activation maps. The technique of visual inspection lacked statistical rigor, but it was helpful in proposing particular regions for the regions of interest (ROI) analysis. Based on visual comparisons of activation maps, both patients and controls showed bilateral activation in the insula, amygdala, and fusiform compared to fixation; furthermore, the patients seemed to show more activation in the insula compared to healthy controls.

For each of the face processing (happy, sad, neutral), healthy controls and patients with schizophrenia appeared to have differences in brain activations (see Figure 3 & 4) but those differences were not significant since the contrast map, or the image of the differences in brain activations, between patients and controls did not yield any significant clusters for any of the 3 emotion conditions (see Figure 5). Adjusting the cluster voxel size from 30 to 0 with threshold maintained at $p < 0.05$, the contrast map between healthy controls and patients, as depicted by the last row of Figure 1, did not yield any significant clusters (not pictured, similar to Figure 5).

Visually, patients showed higher activation of bilateral amygdala during processing of happy faces compared to healthy controls (see Figure 3 & 4). During processing of sad faces, patients showed less deactivation in frontal middle orbital and less activation in right frontal inferior orbital, left putamen, and left hippocampus compared to healthy controls. During processing of neutral faces, patients showed more activation of right frontal mid orbital lobe and more deactivation in right fusiform and bilateral mid-temporal lobe compared to controls. Lastly, during processing of all emotional faces, patients also exhibited higher activation in bilateral
fusiform and less deactivation in right mid-temporal lobe.

Comparisons between happy, sad, and neutral emotion conditions

Patients with schizophrenia did not show significantly different activation during processing of happy faces compared to neutral faces or during processing of sad faces compared to neutral faces; the contrast map between happy and neutral facial processing did not yield any significant clusters and neither did the contrast map between sad and neutral facial processing (see Figure 6). Visually, patients seemed to have little differential insula response to emotion, higher amygdala activation to happy faces compared to sad or neutral faces, and higher fusiform activation to sad faces than to happy or neutral faces.

Similarly, healthy controls did not show significantly different activation during processing of sad faces compared to neutral faces or during processing of sad faces compared to the neutral faces; the contrast map between happy and neutral facial processing did not yield any significant clusters and neither did the contrast map between sad and neutral facial processing (see Figure 7). Visually, however, controls seemed to have higher insular activation during processing of sad faces compared to happy or neutral faces, highest amygdalar activation during processing of neutral faces with sad faces following as higher activation than happy faces, and higher fusiform activation during processing of sad faces compared to either happy or neutral faces.

Comparisons between combined emotions (happy and sad) and neutral facial processing

Patients with schizophrenia did not show significantly different activations during processing of happy and sad faces compared to neutral faces; the contrast map between combined emotions (happy and sad) and neutral facial processing did not yield any significant clusters (see Figure 8). Similarly, healthy controls did not show significantly different activation during processing of happy and sad faces compared to neutral faces; the contrast map between combined
emotions (happy and sad) and neutral facial processing did not yield any significant clusters (see Figure 9). Adjusting the cluster voxel size from 30 to 0 with threshold maintained at p < 0.05, the contrast map between healthy controls and patients, as depicted by the last row of Figure 1, did not yield any significant clusters.

Comparisons between regions of interest (ROIs).

Based on examination of individual activation maps and the literature review of which regions played important roles in emotion processing deficits in schizophrenia as well as emotional face processing in normal controls, bilateral insula, bilateral fusiform gyrus, and bilateral amygdala were selected to be ROIs from automated anatomic labeling atlas in MNI space (see Table 2).

Patterns emerged when comparing the brain activation T values for emotional face processing ROIs (see Table 3). Both patients and healthy controls had more insular activation during processing of sad faces compared to processing happy or neutral faces; controls seemed to have higher insular activation during neutral compared to happy faces whereas patients had less of a difference. Patients had more activation in the amygdala during processing of happy faces compared to sad and neutral whereas controls had more activation in the amygdala during processing of neutral faces compared to happy and sad, although the trends may be obscured by the considerable standard deviations. Both patients and healthy controls had the highest fusiform activation during processing of sad faces compared to happy or neutral faces.

Two-way ANOVA revealed that unlike bilateral amygdala, bilateral insula and fusiform gyrus revealed statistically significant effect of emotional face processing (happy, sad, vs neutral) and/or significant interaction of emotional face processing and subject group (patients with schizophrenia versus healthy controls).

Post hoc paired comparisons were performed to understand the quadratic effects of
emotion (see Table 4). Healthy controls had significantly higher activations in bilateral insula for sad facial processing than for happy facial processing. Aggregates of healthy controls and patients had significantly higher activations in bilateral fusiform for sad facial processing than for happy facial processing; however, examined separately, only healthy controls, not patients, had significantly higher activations for sad facial processing than for happy facial processing. Both healthy controls and patients had significantly stronger activations in bilateral insula for sad facial processing than for neutral processing, with particularly robust significance in patients.

Correlations of Social Cognition Measures to Regional Brain Activation Factor Analysis

A. Social Output

Factor analysis was performed (see methods) to reduce the number of variables to four less correlated factors. Social Output was a factor score that combines scores from the performance-oriented role-play psychometric SSPA, performance-based measure of emotional intelligence MSCEIT, and scales of socially isolating traits (egocentricity and alienation) from BORRTI. In patients with schizophrenia, factor A Social Output was associated with insula deactivation during processing of sad faces ($r=-0.815$, $p<0.001$) and during processing of neutral faces ($r=-0.556$, $p<0.05$) (see figure 10 A). Although the insula correlations of the healthy controls were not statistically significant, healthy controls seem to be associated with activation of insula during processing of sad and neutral faces.

Correlations with contrast maps between emotions were also performed for each ROI. The social output of both patients and controls were associated with significantly higher insular activation in response to processing happy faces compared to sad faces (patient $r=0.815$, control $r=0.783$, $p<0.001$). Patients’ social output was also significantly higher with higher
amygdala activation during processing of happy faces compared to sad faces.

B1. General Social Cognition

Social Cognition was a factor score that combines scores from the inference testing Hinting Task, test of abstracted social scene SAT-MC, and emotion discrimination test BLERT. Though patients seemed to harbor more negative correlations of Social Cognition to insula, amygdala, and fusiform activations than healthy controls, none of the correlations were statistically significant (see figure 10 B1).

B2. Cognitive and Affective Empathy

Cognitive and affective empathy was a factor score that combines scores from Interpersonal Reactivity Index, a self-reported measure of empathy; the scales that were incorporated are Empathic Concern, Fantasy, and Perspective Taking. Patients had a significant correlation with the insula activation difference between happy and neutral facial processing ($r=-0.675, p<0.01$) (see figure 10 B2) and with the amygdala activation difference between happy and sad facial processing ($r=-0.587, p<0.05$). None of the other correlations were statistically significant.

B3. Personal Distress

Personal distress was a factor that’s the scale from Interpersonal Reactivity Index. Patients had a significant correlation with the fusiform activation difference between sad and neutral facial processing ($r=-0.565,p<0.05$) (see figure 10 B3). Controls had a significant correlation with the fusiform activation difference between happy and neutral facial processing ($r=0.773, p<0.01$). None of the other correlations were statistically significant.
Social Skills Performance Assessment (SSPA)

In both patients and healthy controls, none of the correlations between SSPA total score and regional activation or activation differences between emotional face processing was statistically significant (see figure 11).

Bell Object Relations & Reality Testing Inventory (BORRTI)

A. Alienation

On the alienation scale, patients had negative correlations to insula activation for both sad ($r=-0.85, p<0.001$) and neutral facial processing ($r=-0.568, p<0.05$); they had significant correlations to insula activation difference between happy and sad facial processing ($r=0.791, p=0.001$) (see figure 12A). None of the other correlations were statistically significant.

B. Insecure attachment

On the insecure attachment scale, patients had negative correlations to both insula sad ($r=-0.686, p<0.01$) and neutral ($r=-0.625, p<0.05$) facial processing and to both fusiform sad ($r=0.618, p<0.05$) and neutral ($r=-0.605, p<0.05$) facial processing (see figure 12B). They also had significant correlations to the insula activation difference between happy and sad facial processing ($r=0.664, p=0.01$). None of the other correlations were statistically significant.

C. Egocentricity

On the egocentricity scale, patients had negative correlations to both insula sad ($r=0.78, p=0.001$) and neutral ($r=-0.565, p<0.05$) facial processing and significant correlations to insula activation difference between happy and sad ($r=0.785, p=0.001$) facial processing (see figure 12C). Controls had significant correlation to the insula activation difference between happy and sad facial processing ($r=0.638, p<0.05$) and the insula activation difference between
happy and neutral facial processing ($r=0.638$, $p<0.05$).

D. Social Incompetence

On the social incompetence scale, neither patients nor controls had any statistically significant correlations to regional brain activation or activation differences between emotional face processing (see figure 12D). None of the other correlations were statistically significant.

E. Reality distortion

On the reality distortion scale, patients had negative correlation with the insula activation during sad facial processing ($r=-0.769$, $p=0.001$) and a significant correlation with the insula activation difference happy and sad facial processing ($r=0.804$, $p<0.001$) between (see figure 12E). None of the other correlations were statistically significant.

F. Uncertainty of Perception

On the uncertainty of perception scale, patients had negative correlation with insula activation during neutral facial processing ($r=-0.621$, $p<0.05$), amygdala activation during sad ($r=-0.667$, $p<0.05$) and with fusiform activation during both sad ($r=-0.711$, $p<0.01$) and neutral ($r=-0.557$, $p<0.05$) facial processing (see Figure 12F). None of the other correlations were statistically significant.

G. Hallucinations & Delusions

On the hallucinations & delusions scale, patients had no significant correlations to regional brain activation or activation differences. However, controls had correlations to fusiform activation difference between happy and sad ($r=-0.748$, $p<0.05$) (see Figure 12G).
Bell-Lysaker Emotion Recognition Task (BLERT)

Patients had correlations with fusiform activation difference between sad and neutral facial processing ($r=0.578$, $p<0.05$). None of the other correlations were statistically significant (see Figure 13).

Hinting Task

Patients had no statistically significant correlations between hinting task total scores and regional brain activation or activation difference. However, controls had correlation with insula activation difference between happy and sad ($r=-0.727$, $p<0.05$) facial processing and between sad and neutral ($r=0.692$, $p<0.05$) facial processing (see Figure 14).

Revised Eyes Test

Patients had no statistically significant correlations between Eyes Test total score and regional brain activation or activation difference. Controls had correlation with fusiform activation difference between happy and neutral ($r=-0.686$, $p<0.05$) facial processing (Fig 15).

Social Attribution Task- Multiple Choice (SAT-MC)

Patients had no statistically significant correlations between SAT-MC and regional brain activation or activation difference. Controls had correlation with fusiform activation difference between happy and neutral ($r=-0.705$, $p<0.05$) (see figure 16).
Rosenberg Self-Esteem Intake

Patients had positive correlations to insula activation during happy ($r=0.766$, $p<0.001$) and sad facial processing ($r=0.722$, $p<0.01$) and to fusiform activation during sad facial processing ($r=0.594$, $p<0.05$); they also had correlations to insula activation difference between happy and sad facial processing ($r=-0.605$, $p<0.05$). Controls had significant correlations to the insula activation difference between happy and sad facial processing ($r=-0.727$, $p<0.05$) and fusiform activation difference between sad and neutral facial processing ($r=0.692$, $p<0.05$).

NEO Personality Inventory

On the neuroticism scale, patients had significant correlations to the insula activation difference between happy and sad facial processing ($r=0.548$, $p<0.05$). Controls had significant correlations to the fusiform activation difference between sad and neutral facial processing ($r=0.612$, $p<0.05$) (see figure 18A).

On the agreeableness scale, patients had positive correlations to the insula activation during neutral facial processing ($r=0.698$, $p<0.01$) and fusiform activation during sad ($r=0.706$, $p<0.01$) and neutral ($r=0.806$, $p<0.001$) facial processing; they also had significant correlations to the insula activation difference between happy and sad facial processing ($r=0.548$, $p<0.05$) (see figure 18B).

Interpersonal Reactivity Index (IRI) Empathy Intake

There were no patient correlations to IRI’s Perspective Taking scale (see figure 19). On empathic concern scale, patients had correlations to the amygdala activation during happy face processing ($r=-0.605$, $p<0.05$). On the personal distress scale, patients had correlations to the fusiform activation difference between sad and neutral face processing ($r=-0.639$, $p<0.05$). On the fantasy scale, patients had significant correlations to the insular activation during happy,
amygdalar activation during neutral, and insula activation difference between happy and neutral.

Maloy-Salovey-Caruso Emotional Intelligence Test (MSCEIT)

Patients had significant correlations to the insula activation difference between happy and sad facial processing ($r=-0.551$, $p<0.05$) (see figure 20).
Discussion

Overall impression

This was the first report on the correlation of social cognitive psychometrics to functional MRI regional brain activation in amygdala, fusiform gyrus, and insular cortex during passive viewing of happy, sad, and neutral faces from Gur’s University of Pennsylvania series in patients with schizophrenia.

The results from our imaging paradigm were consistent with previous studies. A meta-analysis of 105 fMRI studies in healthy controls in an effort to generate a reliable normative map of brain response from activation likelihood estimations showed that during processing of emotional and neutral faces, there were increased activation in visual areas including fusiform gyrus, limbic areas including amygdala, and temperoparietal areas including insula compared to baseline (Fusar-Poli et al 2009). Healthy controls did exhibit differences in activation when processing emotional faces in comparison to when processing neutral faces; in particular, both processing of happy and sad faces displayed higher amygdala activation compared to processing of neutral faces. Comparing happy and sad revealed no significant clusters on contrast maps in the Fusar-Poli et al study, consistent with findings from this study.

Interestingly, healthy controls did not exhibit sensitivity to emotion compared to neutral in the amygdala--while this differs from the general conclusions of the meta-analysis, it must be noted that Fusar-Poli et al found significant differences in studies that used implicit emotional processing versus explicit emotional processing. Explicit emotional processing would involve active and conscious emotion discrimination and has been found to engage more of temporal part of fusiform gyrus and bilateral amygdala compared with implicit emotional processing. Implicit emotional processing would involve passive viewing of faces and has been found to engage more of the occipital part of fusiform gyrus and insula. The present study utilized implicit processing for the subjects were asked to passively view the faces without being asked to discriminate
between face emotions. The present ROI analysis yielded emotional sensitivities in fusiform and insula but not in amygdala—this finding may very well be related to the nature of the implicit emotional processing. There may not be enough statistical power to detect amygdala sensitivity to emotion though there was enough to detect emotional sensitivities in ROIs that are more engaged in implicit emotional processing. Furthermore, the majority of studies that show significant abnormalities in amygdala activation were during processing of fearful faces—an emotion which we did not incorporate into our study.

Based on contrast maps, we did not find statistically significant differences between patients and healthy controls. Although not statistically significant, visual inspection suggested a general pattern: while both patients and controls seemed to show bilateral activation in the insula, amygdala, and fusiform compared to fixation, patients seemed to show more activation in insula though less in amygdala and fusiform compared to healthy controls. These general patterns were confirmed by ROI analysis—a tool which also added more informative results regarding the differences between patients and controls across emotions: Healthy controls showed significantly higher activation in the insular cortex during processing of sad faces compared to happy faces while patients did not show a difference between emotions. Both subject groups showed higher activation in the fusiform gyrus during processing of sad faces compared to happy faces and significantly higher activation during processing of sad faces compared to neutral face. Interestingly, controls had significantly higher fusiform activations during processing of sad faces compared to happy faces while patients had the same pattern but did not approach statistical significance.

Overall, patients seemed to have marked hypo-activations in amygdala and fusiform and less activation differences in insula compared to controls; in each ROI, the differences between emotional processing seemed to be blunted in patients compared to controls. This differential
activation of patients versus controls is also consistent with previous studies. A meta-analysis in patients with schizophrenia based on activation likelihood estimates from 17 fMRI studies found that while both patients with schizophrenia and healthy controls activated amygdala and fusiform gyrus, the activation was lower in patients with schizophrenia (Li et al 2010). In the meta-analysis, patients had slightly higher activation in the left insula compared to controls. In a fMRI study by Habel et al, patients viewing basic emotional faces of happy, sad, angry, and fearful were characterized by mostly hypo-activations across amygdala, fusiform, and insula compared to controls; patients viewing neutral faces were characterized by hypo-activation in fusiform and parts of temporal cortex compared to controls (Habel et al in 2010). To date, there has not been a meta-analysis in patients with schizophrenia that had commented on the sensitivity to emotion in the patient group, including specifically the differential activation in response to the basic emotions of happy, sad, and neutral, likely due to the difficulty of detecting these sensitivities in a typical fMRI study. In fMRI studies focused on the amygdala, the blunted difference in patients with schizophrenia’ brain activation response to fearful faces and neutral faces has been explained primarily by the effect of neutral faces in raising activation from baseline whereas neutral faces do not had hyperactive effects in healthy controls. In the present study, neutral faces did not seem to exhibit similar hyperactive effects in patients with schizophrenia compared to controls.

Patients with schizophrenia scored significantly lower on SSPA, Hinting Task, Rosenberg Self-Esteem Intake, and NEO agreeableness scale as well as significant higher on 6/7 BORRTI dimensions—alienation, insecure attachment, egocentricity, social incompetence, reality distortion, and hallucinations & delusions—and NEO neuroticism scale. Factor analyses reduced to the psychometrics to 4 dimensions—social output, general social, cognitive and affective empathy, and personal distress. Of those, social output corresponded the most to
patients’ insular cortex activation during sad ($r=-0.815, p<0.001$) and neutral ($r=-0.556, p<0.05$) facial processing and to patients’ insular ($r=0.815, p<0.001$) and fusiform ($r=0.631, p<0.05$) activation difference between happy and sad facial processing. Cognitive & affective empathy correlated to insular cortex activation difference between viewing happy and neutral faces ($r=0.675, p<0.05$) and personal distress corresponded to fusiform activation difference between sad and neutral ($r=0.565, p<0.05$). These results suggest that Social Output, having strong neural correlates, may be a useful dimension in understanding social cognition.

Individual correlations with psychometrics and regional brain activation & activation differences across processing of emotional stimuli offered more input on the utility of factor scores. SSPA showed no significant correlations to fusiform and insular activation, signifying that it may be unnecessary to include this in the Social Output factor altogether. Of the psychometrics, BORRTI was the most interesting in yielding significant correlations between patient regional activation and psychometric scales, with the exception of the social incompetence scale although the hallucinations & delusions scale does not offer meaningful information regarding patients’ regional activation. The results from BLERT were as expected—this was a test that should most engage the fusiform gyrus as the examinees are focused on faces. Happy was a relatively easy emotion to discriminate while sad was much more challenging to distinguish from neutral; thus, it was not surprising that patients’ high performance on BLERT corresponded to his or her inherent differential response to sad versus neutral faces.

The Revised Eyes Test, SAT-MC, and Hinting Task did not yield any informative correlations regarding patients’ regional activation. Revised Eyes Test and SAT-MC yielded significant correlations for healthy controls’ regional activation; both tests were actually quite challenging, even for healthy controls, and the patients’ scores were not significantly lower than
the control’s scores. Hinting Task hinged more on intention inference, a Theory of Mind trait that may be a distinct process from facial emotional processing altogether—it was entirely conceivable that patients with schizophrenia had inherent deficits in emotional face processing but possessed the ability to infer the correct intention when given the appropriate “perception” through verbal cues; moreover, tasks of intention inference may be surmountable with a higher IQ and help of other nonsocial cognitive skills while emotional face processing is less so.

The Rosenberg Self-Esteem Intake yielded interesting results. High self-reported self-esteem was associated with higher activation in the insula and fusiform during emotional face processing as well as a higher activation difference between happy and sad. This suggested that patients with schizophrenia with higher self-esteem had less blunted activation response to emotional face stimuli and may be more functional socially. NEO Personality Inventory’s agreeableness yielded similar correlations. If a patient with schizophrenia scored higher on the agreeableness scale, he or she also had less blunted activation responses to emotional face stimuli.

Conclusions & Future Directions

Taken together, these findings were encouraging for the ecological validity of neuroimaging methodology commonly used in many previous research efforts on emotional face processing. These findings were also promising for the meaningful capture of certain social cognitive psychometrics such as BLERT, BORRTI, Rosenberg Self-Esteem, and NEO Personality Inventory. As expected, BLERT, a test of facial affect discrimination, corresponded to fusiform gyrus regional activation. Although BORRTI, Rosenberg Self-Esteem, and NEO Personality Inventory were not directed towards facial affect discrimination, high scores on those measures were nevertheless indicative of a more socially capable individual who may not have as
apparent deficit in emotional face processing. The Factor Analyses was particular useful in reducing the number of variables studied although further dissection will be needed regarding the significance of Interpersonal Reactivity Index and MSCEIT which are each a part of a distinct factor score. It is conceivable to refine a neurocognitive battery for patients with schizophrenia one day that will not only have significant correlations to clinical outcomes, functional outcomes, but also to frank brain activation patterns.

Limitations

There were a number of limitations to this study. The main limitations were typical to fMRI studies in that there sample size is small and the statistical power would ideally have been higher to detect more sensitivities to emotion and subject group. The community comparison sample was not ideal. There were a higher proportion of males to females. Because of the limited statistical power of the study, we could not control for age, sex, schizophrenia diagnosis, and other possible modifiers. Another potential problem was that the patient population included both paranoid schizophrenia and schizoaffective disorder and it was unclear how different fMRI regional activation during emotional face processing would be in patients with one diagnosis versus the other.

Some subjects recruited from the urban setting of New Haven may also be not fMRI naïve; particularly, patients with schizophrenia may often return as subjects. Having been in a fMRI before may be a significant confounding as anxiety responses may hide potential hypo-activation of certain regions of interests during emotional face processing. Finally, the interpretation of the significant correlations between social cognition measures and regional activation during emotional face processing would have been improved had we also tested the correlations between non-social cognition measures (i.e. general cognition measures) and regional
activation of our 3 ROIs and the correlations between social cognition measures and regional activation of a non-related region, such as part of the olfactory cortex.
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Table 1. Participant Characteristics for Demographic, Clinical, and Social Cognitive Measures (N=25)

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<td>Paranoid</td>
<td>9 (64.0%)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Residual</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>5 (36.0%)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Psychosis disorder NOS</td>
<td>0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td>8 (57.1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Conventional</td>
<td>3 (21.4%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>2 (14.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (7.1%)</td>
<td>11 (100%)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age</td>
<td>43.8 (9.7)</td>
<td>46.5 (9.9)</td>
<td>40.3 (8.6)</td>
</tr>
<tr>
<td>Years of Education *</td>
<td>14.2 (2.2)</td>
<td>13.1 (2.1)</td>
<td>15.5 (1.6)</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>25.0 (7.2)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Lifetime # of Hospitalizations</td>
<td>8.3 (5.8)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Past Full-time Jobs</td>
<td>2.4 (2.4)</td>
<td>2.2 (2.8)</td>
<td>2.8 (1.4)</td>
</tr>
<tr>
<td>Socialization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Friends</td>
<td>6.2 (3.3)</td>
<td>5.5 (3.4)</td>
<td>7.1 (3.2)</td>
</tr>
<tr>
<td># Acquaintances</td>
<td>5.6 (3.2)</td>
<td>5.1 (3.4)</td>
<td>6.2 (3.3)</td>
</tr>
<tr>
<td># Community Members *</td>
<td>4.5 (3.0)</td>
<td>3.4 (2.7)</td>
<td>5.9 (2.8)</td>
</tr>
<tr>
<td># Family Members</td>
<td>6.9 (3.1)</td>
<td>6.6 (3.1)</td>
<td>7.3 (3.1)</td>
</tr>
<tr>
<td># Partners</td>
<td>4.5 (4.4)</td>
<td>3.4 (4.1)</td>
<td>5.9 (4.6)</td>
</tr>
<tr>
<td># Other *</td>
<td>6.1 (3.0)</td>
<td>4.6 (2.9)</td>
<td>8.0 (1.9)</td>
</tr>
<tr>
<td>PANSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>67.1 (19.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>19.6 (6.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16.2 (6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>31.3 (11.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
<td>Comparison</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Quality of Life **</td>
<td>80.5 (27.7)</td>
<td>61.7 (18.9)</td>
<td>106.7 (11.8)</td>
</tr>
<tr>
<td>Social cognition measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSPA *</td>
<td>73.2</td>
<td>68.2</td>
<td>79.6</td>
</tr>
<tr>
<td>BORRTI alienation*</td>
<td>52.1</td>
<td>56.2</td>
<td>46.3</td>
</tr>
<tr>
<td>BORRTI insecure attachment *</td>
<td>49.6</td>
<td>55.0</td>
<td>42.0</td>
</tr>
<tr>
<td>BORRTI egocentricity **</td>
<td>54.3</td>
<td>61.1</td>
<td>44.6</td>
</tr>
<tr>
<td>BORRTI social incompetence *</td>
<td>50.4</td>
<td>53.4</td>
<td>46.1</td>
</tr>
<tr>
<td>BORRTI reality distortion *</td>
<td>54.0</td>
<td>61.6</td>
<td>43.5</td>
</tr>
<tr>
<td>BORRTI uncertainty of perception</td>
<td>49.9</td>
<td>53.2</td>
<td>45.3</td>
</tr>
<tr>
<td>BORRTI hallucinations &amp; delusions **</td>
<td>58.5</td>
<td>67.6</td>
<td>45.8</td>
</tr>
<tr>
<td>BLERT-score correct</td>
<td>14.8</td>
<td>14.0</td>
<td>15.9</td>
</tr>
<tr>
<td>Hinting Task *</td>
<td>18.0</td>
<td>17.1</td>
<td>19</td>
</tr>
<tr>
<td>Revised Eyes Test</td>
<td>64.3</td>
<td>62.5</td>
<td>66.7</td>
</tr>
<tr>
<td>SAT-MC-score correct</td>
<td>13.9</td>
<td>12.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Rosenberg Self-Esteem Intake *</td>
<td>37.6</td>
<td>33.5</td>
<td>42.9</td>
</tr>
<tr>
<td>NEO neuroticism *</td>
<td>23.2</td>
<td>27.8</td>
<td>17.6</td>
</tr>
<tr>
<td>NEO extroversion</td>
<td>28.7</td>
<td>27.5</td>
<td>30.2</td>
</tr>
<tr>
<td>NEO openness</td>
<td>28.3</td>
<td>26.6</td>
<td>30.5</td>
</tr>
<tr>
<td>NEO agreeableness *</td>
<td>32.7</td>
<td>30.4</td>
<td>35.7</td>
</tr>
<tr>
<td>NEO conscientiousness</td>
<td>31.0</td>
<td>30.9</td>
<td>31.2</td>
</tr>
<tr>
<td>IRI Perspective Taking *</td>
<td>16.0</td>
<td>14.1</td>
<td>18.4</td>
</tr>
<tr>
<td>IRI Empathic Concern</td>
<td>18.7</td>
<td>18.5</td>
<td>18.9</td>
</tr>
<tr>
<td>IRI Personal Distress</td>
<td>11.9</td>
<td>11.8</td>
<td>12.0</td>
</tr>
<tr>
<td>IRI Fantasy</td>
<td>12.9</td>
<td>12.4</td>
<td>13.6</td>
</tr>
<tr>
<td>MSCEIT *</td>
<td>38.3</td>
<td>28.2</td>
<td>27.9</td>
</tr>
</tbody>
</table>

Note: PANSS, Positive and Negative Symptom Scale; SSPA, Social Skills Performance Assessment; BORRTI, Bell Object Relations & Reality Testing Inventory; SAT-MC, Social Attribution Task-Multiple Choice; BLERT, Bell Lysaker Emotion Recognition Test; NEO, Personality Intake; IRI, Interpersonal Relativity Index; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test. * indicates $p < 0.05$; ** indicates $p < 0.001$ in the t-test comparison of patients to controls.
Figure 1. Emotional Faces

Design and examples of stimuli presented under fMRI; participants were asked to judge whether the emotional face displayed was female or male.

Figure 2. Comparison of Patients with Schizophrenia and Healthy Controls During Processing of Happy, Sad, and Neutral Emotion

Warmer colors in the ROYGBIV spectrum represent activation while cooler colors (blue) represent deactivation and gray is the level of activation established from fixation (human faces > fixation, cluster p < 0.05).  
A. Patients brain activations for all emotion conditions (happy, sad, neutral).  
B. Control brain activations for all emotion conditions.  
C. Contrast map of patient and control, or the difference in brain activation between patient and controls for all emotion conditions.
Warmer colors in the ROYGBIV spectrum represent activation while cooler colors (blue) represent deactivation and gray is the level of activation established from fixation (human faces > fixation, cluster p < 0.05). A. Patients brain activations during processing of happy faces. B. Patient brain activations during processing of sad faces. C. Patient brain activations during processing of neutral faces. Pictured are samples axial slices, all at a threshold of p < 0.05.
Figure 4. Comparison of Happy, Sad, and Neutral Facial Processing for Healthy Subjects

Warmer colors in the ROYGBIV spectrum represent activation while cooler colors (blue) represent deactivation and gray is the level of activation established from fixation (human faces > fixation, cluster p < 0.05). A. Control brain activations during processing of happy faces. B. Control brain activations during processing of sad faces. C. Control brain activations during processing of neutral faces. Pictured are samples axial slices, all at a threshold of p < 0.05.
Differential neurofunctional response to emotions. A. Contrast map of patient & control brain activations, or the image of differences in brain activations between patient and control participants, during processing of happy faces. B. Contrast map of patient & control brain activations during processing of sad faces. C. Contrast map of patient & control brain activations during processing of neutral faces. Pictured are samples axial slices, all at a threshold of $p < 0.05$, cluster size of 30. Note, however, the images of $p < 0.05$, cluster size of 0 did not appear significantly different.
Figure 6. Contrast Maps of Happy and Neutral Facial Processing and of Sad and Neutral Facial Processing in Patients with Schizophrenia

A. Happy - Neutral

B. Sad - Neutral

A. Contrast map, or difference between brain activations during processing of happy and neutral faces in patients with schizophrenia. B. Contrast map of sad and neutral facial processing in patients with schizophrenia. Pictured are samples axial slices, all at a threshold of $p < 0.05$, cluster size of 30. Note, however, the images of $p < 0.05$, cluster size of 0 did not appear significantly different.

Figure 7. Contrast Maps of Happy and Neutral Facial Processing and of Sad and Neutral Facial Processing in Healthy Controls

A. Happy - Neutral

B. Sad - Neutral

A. Contrast map, or difference between brain activations during processing of happy and neutral faces in healthy controls. B. Contrast map of sad and neutral facial processing in healthy controls. Pictured are samples axial slices, all at a threshold of $p < 0.05$, cluster
size of 30. Note, however, the images of $p < 0.05$, cluster size of 0 did not appear significantly different.

Figure 8. Comparison of Combined Happy and Sad Facial Processing to Neutral Facial Processing in Patients with Schizophrenia

A. Aggregate image of patients’ brain activation during processing of happy and sad faces. B. Patients’ brain activation during processing of neutral faces. C. Contrast map between combined emotions (happy & sad) and neutral face processing in patients. Pictured are sample axial slices, all at a threshold of $p < 0.05$, cluster size of 30. Note, however, the images of cluster size = 0, $p < 0.05$ did not appear significantly different.
Figure 9. Comparison of Combined Happy and Sad Facial Processing to Neutral Facial Processing in Healthy Controls.

A. Aggregate image of controls’ brain activation during processing of happy and sad faces. B. Controls’ brain activation during processing of neutral faces. C. Contrast map between combined emotions (happy & sad) and neutral face processing in controls. Picture are sample axial slices, all at a threshold of p < 0.05, cluster size of 30. Note, however, the images of cluster size = 0, p < 0.05 did not appear significantly different.

Table 2. Region of Interest (ROI) Characteristics

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>Brodmann area</th>
<th>Peak Voxel x</th>
<th>y</th>
<th>z</th>
<th>Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insula L</td>
<td>13</td>
<td>47</td>
<td>7</td>
<td>-1</td>
<td>21342</td>
</tr>
<tr>
<td>Insula R</td>
<td>44</td>
<td>-41</td>
<td>4</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>Fusiform L</td>
<td>19</td>
<td>39</td>
<td>-50</td>
<td>17</td>
<td>54020</td>
</tr>
<tr>
<td>Fusiform R</td>
<td>37</td>
<td>-42</td>
<td>-47</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Amygdala L</td>
<td>Amy</td>
<td>22</td>
<td>1</td>
<td>-24</td>
<td>4739</td>
</tr>
<tr>
<td>Amygdala R</td>
<td>Amy</td>
<td>-18</td>
<td>1</td>
<td>-24</td>
<td></td>
</tr>
</tbody>
</table>

L = left; R = right; voxels = volume in mm$^3$. Cluster p < 0.05. Amy = amygdala; note that various Brodmann areas compose amygdala as well as other functional regions.
Table 3. Brain Activation T during Processing of Happy, Sad, and Neutral Faces

<table>
<thead>
<tr>
<th></th>
<th>T during Happy (SD)</th>
<th>T during Sad (SD)</th>
<th>T during Neutral (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Insula ***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.019 (0.377)</td>
<td>0.033 (0.033)</td>
<td>0.025 (0.029)</td>
</tr>
<tr>
<td>Patients</td>
<td>0.024 (0.033)</td>
<td>0.026 (0.037)</td>
<td>0.020 (0.026)</td>
</tr>
<tr>
<td>Controls</td>
<td>0.011 (0.043)</td>
<td>0.041 (0.024)</td>
<td>0.031 (0.032)</td>
</tr>
<tr>
<td><strong>Amygdala</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.041 (0.130)</td>
<td>0.035 (0.280)</td>
<td>0.048 (0.125)</td>
</tr>
<tr>
<td>Patients</td>
<td>0.044 (0.161)</td>
<td>0.025 (0.127)</td>
<td>0.039 (0.152)</td>
</tr>
<tr>
<td>Controls</td>
<td>0.036 (0.081)</td>
<td>0.049 (0.134)</td>
<td>0.059 (0.085)</td>
</tr>
<tr>
<td>**Fusiform ***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.055 (0.064)</td>
<td>0.085 (0.066)</td>
<td>0.054 (0.058)</td>
</tr>
<tr>
<td>Patients</td>
<td>0.052 (0.070)</td>
<td>0.072 (0.059)</td>
<td>0.042 (0.054)</td>
</tr>
<tr>
<td>Controls</td>
<td>0.057 (0.059)</td>
<td>0.101 (0.073)</td>
<td>0.068 (0.062)</td>
</tr>
</tbody>
</table>

T = beta activation measure. * Next to ROI indicates ANOVA detected either statistically significant (p<0.05) effect of emotion or effect of interaction between emotion and subject group.

Table 4. P-values from Tukey Post-hoc Comparisons for Paired Emotional Facial Processing in Insula and Fusiform ROIs

<table>
<thead>
<tr>
<th></th>
<th>Happy - Sad</th>
<th>Happy - Neutral</th>
<th>Sad - Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insula</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.078</td>
<td>0.339</td>
<td>0.146</td>
</tr>
<tr>
<td>Patients</td>
<td>0.896</td>
<td>0.599</td>
<td>0.451</td>
</tr>
<tr>
<td>Controls</td>
<td>0.032 *</td>
<td>0.057</td>
<td>0.180</td>
</tr>
<tr>
<td><strong>Fusiform</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.023 *</td>
<td>0.920</td>
<td>0.001**</td>
</tr>
<tr>
<td>Patients</td>
<td>0.269</td>
<td>0.481</td>
<td>0.009 *</td>
</tr>
<tr>
<td>Controls</td>
<td>0.037 *</td>
<td>0.602</td>
<td>0.038 *</td>
</tr>
</tbody>
</table>

All values are p values; * indicates p < 0.05 and ** indicates p < 0.001. All indicates patients with schizophrenia combined with healthy controls.
The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold p< 0.05.
B1. General Social

Red = patient; Blue = Control. Threshold p< 0.05.


Red = patient; Blue = Control. Threshold p< 0.05.
B3. Personal Distress

Red = patient; Blue = Control. Threshold p< 0.05.
The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold p< 0.05.
Figure 12. BORRTI
A. Alienation

The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold p< 0.05.
B. Insecure Attachment

Red = patient; Blue = Control. Threshold p< 0.05.

C. Egocentricity

Red = patient; Blue = Control. Threshold p< 0.05.
D. Social Incompetence

Red = patient; Blue = Control. Threshold p< 0.05.

E. Reality Distortion

Red = patient; Blue = Control. Threshold p< 0.05.
F. Uncertainty of Perception

Red = patient; Blue = Control. Threshold p< 0.05.

G. Hallucinations & Delusions

Red = patient; Blue = Control. Threshold p< 0.05.
Figure 13. Correlations between BLERT and regional brain activation for processing of emotional faces and for contrast maps between emotional faces

The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold p< 0.05.
Figure 14. Hinting Task

The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold $p < 0.05$. 
The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold $p< 0.05$. 
Figure 16. SAT-MC (Total Score)

The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold p< 0.05.
Figure 17. Rosenberg Self-Esteem Intake

The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold p< 0.05.
Figure 18. NEO-Personality Intake
A. Neuroticism

The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold p< 0.05.
B. NEO Agreeableness

Red = patient; Blue = Control. Threshold p< 0.05.
Figure 19. IRI Empathy
A. Perspective Taking

The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold p< 0.05.
B. Empathic Concern

Red = patient; Blue = Control. Threshold $p < 0.05$.

C. Personal Distress

Red = patient; Blue = Control. Threshold $p < 0.05$. 

Page 76
D. Fantasy

Red = patient; Blue = Control. Threshold p< 0.05.
The brightened embossed bar with the adjacent label (value = correlation coefficient) signifies that it is a significant correlation; the lighter unembossed bars without adjacent labels are not significantly significant. Red = patient; Blue = Control. Threshold $p<0.05$. 

Figure 20. Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)