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Beyond the Kraepelinian Dichotomy: Investigation into Neural Phenotypes of Schizophrenia and Bipolar Disorder

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Beyond the Kraepelinian Dichotomy:

Investigation into Neural Phenotypes of Schizophrenia and Bipolar Disorder

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Psychology

by

Amy Marie Jimenez

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ABSTRACT OF THE DISSERTATION

Beyond the Kraepelinian Dichotomy:

Investigation into Neural Phenotypes of Schizophrenia and Bipolar Disorder

by

Amy Marie Jimenez

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2013

Professor Matthew D. Lieberman, Chair

Current classification systems of mental illness characterize bipolar disorder (BD) and schizophrenia (SCZ) as discrete diagnostic categories, presupposing distinct presentation, etiology, and treatment, despite mounting evidence of epidemiological and genetic overlap between the two and in a way that does not fully reflect increasing knowledge of underlying biological mechanisms or pathogenesis. To further elucidate the nature of phenotypic overlap versus differentiation between the two, emotion perception and regulation deficits were examined via a task of affect recognition during fMRI. Data were collected at the Karolinska Institute in Sweden; demographically matched participants were recruited based on national medical records data in line with study protocol approved by Karolinska and UCLA IRB.

Behaviorally, patients with SCZ (n=41) and BD (n=38) demonstrated similar impairment in affect labeling relative to controls (n=64); however, SCZ patients showed greater deficits during affect matching and the two groups showed differences in corresponding patterns of neural activation. During affect matching, whole-brain voxel-wise BOLD signal analysis indicated both patient groups showed hypoactivation relative to controls in putative social cognitive network regions but the specific regions differed by group, such that BD patients showed hypoactivation of posterior cingulate/precuneus, whereas SCZ patients showed hypoactivity in right amygdala/hippocampus. In addition, the SCZ group demonstrated failure of fronto-limbic circuitry to modulate ventral face and emotion processing regions during affect labeling; they showed hyperactivation of fusiform gyrus, inferior occipital cortex, and posterior superior and middle temporal gyrus and did not show negative functional connectivity between these regions as shown in controls and BD patients through PPI analysis. SCZ patients also showed aberrant positive cortico-cortical connectivity in frontal regions versus BD patients, suggestive of compensatory recruitment of additional frontal regions. The current study thus adds new and novel evidence to the ongoing debate regarding the utility of categorical classification of disease, demonstrating underlying disparateness in neurophysiology related to specific aspects of the socio-emotional domain and lending at least partial validation to the current diagnostic distinction. Implications for treatment considerations are also discussed.

The dissertation of Amy Marie Jimenez is approved.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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I. INTRODUCTION

For over a century, the field of psychiatry has utilized a categorical approach to identify, diagnose, and classify mental illness. This taxonomy is reflected in the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), in which schizophrenia (SCZ) and bipolar disorder (BD) are operationalized according to a historically accepted Kraepelinian dichotomy as two discrete disease states (Kraepelin, 1921). This distinction is based largely on differences in symptom profile and outcome; differences in underlying biological mechanisms or etiology do not currently play a major role in psychiatric differentiation. However, researchers are now beginning to question the validity of the traditional nosology, moving toward a more dimensional approach in recognition of clinically relevant features that cut across diagnostic categories. In fact, a primary agenda item of the DSM 5 Task Force was to better integrate categorical and dimensional assessment criteria (Regier, Narrow, Kuhl, & Kupfer, 2009). Although in the end DSM-V will retain categorical diagnostic classification, the National Institute of Mental Health (NIMH) has further pushed for a dimensional approach with its emphasis on alternative Research Domain Criteria (RDoC) and lack of support for research based solely on DSM criteria (NIMH, 2013).

There is mounting evidence of epidemiological (Berretini, 2004), clinical (Lin & Mitchell, 2008), and genetic (Berrettini, 2000; Farmer, Elkin, & McGuffin, 2007; Lichtenstein et. al., 2008; Moskvina et. al., 2009; Ivleva, Thaker, & Tamminga, 2008) overlap between SCZ and BD. For example, in a population-based genetic epidemiological study of 2 million nuclear families in Sweden, about one-half of the genetic component of SCZ was found to overlap with that of BD, and about two-thirds of the genetic component of BD was found to overlap with that of SCZ (Lichtenstein et. al., 2008). Behavioral geneticists and clinical neuroscientists have

conducted further investigations into this overlap, focusing on intermediate phenotypes that may occur as continuous dimensions which span affective and nonaffective disorders. Proposed endophenotypes that have garnered the most attention in research to date include psychosis susceptibility (Craddock, O'Donovan, & Owen, 2006; Potash, Willour, Chiu, Simpson, et. al., 2001) and neurocognitive impairment (Cannon, Huttunen, Lonnqvist, Tuulio-Henriksson, Pirkola, et. al., 2000; Jabben, Arts, Krabbendam, & van Os, 2009), although neuroanatomical markers (Yu, Cheung, Leung, li, Chua, & McAlonan, 2010; Bearden, van Erp, Thompson, Toga, & Cannon, 2007), and affective disturbance (Krabbendam, et. al., 2005) have received attention as well. If SCZ and BD share a pool of underlying genetic propensities in common, genes involving other potentially pathogenic processes (e.g., related to disrupted neurodevelopment) as well as environmental factors may then interact differentially with this common pool of susceptibility genes to account in part for differences observed between these disorders (Murray, et. al., 2004; Jabben, et. al., 2009). However, empirical examples of this complex interactive process resulting in phenotypic heterogeneity have not yet been elucidated.

In fact, it is not clear how many aspects of the phenotypic profiles of these disorders might fit in to this model, and whether they exemplify dimensional overlap or differentiation. In particular, emotion-processing deficits are central clinical features of both SCZ and BD for which there may or may not be overlap neurobiologically. Individuals with SCZ show marked impairments in perception of emotional stimuli and blunted emotional expressivity (Edwards, Pattison, Jackson, & Wales, 2001; Shtasel, Gur, Gallacher, Heimberg, Cannon, & Gur, 1992), and BD is characterized by emotion dysregulation and impulsivity (Swann, Pazzaglia, Nicholls, Dougherty, Moeller, 2003). Although an abundance of literature has described select aspects of these deficits, neural correlates of these phenotypic profiles remain unclear. Given that emotional

information processing requires a comprehensive yet cohesive response set acting within a dynamic social context, such abilities likely rely upon distributed neural systems dependent on both short- and long-range connectivity. Observable deficits in specific socio-emotional skills likely implicate disruptions in such systems, either via regional failures, break down of connectivity between networks, or both. Whether these disruptions are similar across SCZ and BD and reflect identical or distinct pathogenic mechanisms has not yet been explicitly tested.

Importantly, this area of inquiry may have significant clinical implications. Social functioning is increasingly recognized as an important outcome measure in both SCZ and BD research (Lenior, Dingemans, Linszen, De Haan, & Schene, 2001; Malkoff-Schwartz et. al.,1998), impacting medication adherence, relapse and hospitalization rates, and quality of life measures (Gearing, 2008; Lam et. al., 2007; Beynon et. al., 2008; Miklowitz et. al., 2003). Elucidating the precise mechanisms of social functioning deficits may thus provide targets for more effective treatment.

Toward these ends, I proposed to investigate the disruption of specific aspects of socio-emotional information processing in SCZ and BD for my dissertation program of research. Specifically, the aim of the current project was to examine the associated neural systems involved in deficits of emotion perception and incidental emotion regulation, including both discrete regions of interest and neural networks reliant on connectivity and coordinated action between regions. To do so, basic science literature on the organization of socio-emotional processes was referenced and a task drawn from this field was translated for use in a functional neuroimaging study of patients with SCZ and BD and matched controls. I sought to ascertain whether socio-emotional processing deficits constitute examples of phenotypic overlap between SCZ and BD, consistent with a dimensional intermediate phenotype model, or of phenotypic

differentiation, useful for categorical classification of disorder. Furthermore, the relationship between these neurally mediated deficits and symptomatic and functional outcomes, as well as variation in course of illness and medication exposures, was assessed to inform relevant clinical considerations.

II. LITERATURE REVIEW

2.1. Socio-Emotional Disruptions in Severe Mental Illness

Social functioning deficits are among the primary and most debilitating features of both SCZ and BD, with varying degrees of similarity evident in the overt manifestation of specific deficits in the two disorders. Emotion is conceptualized as involving several different components, including perception, expression, experience, and regulation (cf., Plutchik, 1984; Russell, 2003, Phillips, Drevets, Rauch, & Lane, 2003a). As mentioned, emotion perception and emotion regulation, in particular, may be implicated in impairments of the socio-emotional domain in SCZ and BD. Emotion perception is thought to involve the identification and appraisal of a stimulus as salient or self-significant, beyond that of non-emotional stimuli (Campos, Frankel, & Camras, 2004; LeDoux, 2000). This can occur at both conscious and unconscious levels (Lazarus, 1991), and the activating stimuli may be either external or internal (i.e., a mental representation) in nature. Emotion perception cues us in to dangers and threats from our environment and those around us and facilitates the maintenance and enhancement of pleasurable or otherwise favorable experiences and relationships. Emotion regulation refers to the deliberate or incidental modulation and/or inhibition of emotional processes which may occur at any or all emotion stages, but which effectively alters our emotional experience. Emotion regulation is

important for ensuring the contextual appropriateness of our affective states and subsequent behavior (e.g., Ochsner & Gross, 2005).

2.1a. Socio-Emotional Disruptions in Schizophrenia

Socio-emotional disruptions in SCZ are well established, impacting many different aspects of the emotion processing stream. For example, blunted emotional expressivity is a prominent feature of the disorder and has been described extensively (e.g., Krause, Steimer, Sanger-Alt, & Wagner, 1989). Interestingly, impairment in expression of emotion does not seem to implicate diminution of the corresponding emotion experience (Kring, 1993; Berenbaum & Oltmanns, 1992) but has been found to significantly predict impaired emotion perception (Gur, Kohler, Ragland, Siegel, Lesko, et. al., 2006). Emotion perception, in particular, has received a great deal of attention in the experimental literature, with conflicting findings (e.g., Edwards, Jackson, & Pattison, 2002).

Many studies have indicated that individuals with SCZ have difficulty identifying emotion from faces. However, concurrent deficits in elements of basic face processing, especially identity recognition, have led some to conclude that poor performance on emotion recognition tasks reflects a more generalized deficit in perception of faces, perhaps owing to broad-spectrum cognitive impairments (e.g., Kerr & Neale, 1993; Mueser, Doonan, Penn, Blanchard, Bellack, et. al., 1996). Still, others argue for evidence of differential impairment in emotion perception (Kosmidis, Bozikas, Giannakou, Anezoulaki, Fantie, et. al., 2007). For example, Gooding, Luh, and Tallent (2001) found evidence for intact processing of other kinds of information gleaned from faces, such as gender or age, but greater relative difficulty processing emotional information from faces. Hooker and Park (2002) found selectively impaired performance for emotional versus neutral faces on an affect-matching task across

emotion types in SCZ patients relative to controls, likewise suggesting a selective deficit; however, the patients were also impaired on an identity recognition task, evidence of a general deficit. Importantly, many of these studies of emotional face perception (e.g., Kerr & Neale, 1993; Mueser et. al., 1996; Addington & Addington, 1998; Hooker & Park, 2002) utilized the Benton and Van Allen Test of Facial Recognition (1975) as the control task to ascertain whether results indicate selective difficulties with emotion perception or difficulty with faces in general. Such methodological consistency has the advantage of allowing for comparison across studies. However, a review by Edwards et. al. (2002) notes that the Benton and Van Allen Test appears to have been more difficult than the emotion tasks in those studies and that conclusive assessment of "extra" or differential impairments requires comprehensive matching of tasks on basic difficulty. Even subtle differences between tasks, including variations in stimulus intensities, number and complexity of stimuli on screen, and number of forced choice options are all details that may impact performance, especially in cognitively impaired patients.

Several studies have attempted to address these concerns. For example, one study utilized two simple matching tasks: 3-item forced choice emotion expression versus facial orientation discriminations, with no language or memory demands. SCZ patients were significantly worse on both tasks than healthy controls (Doop & Park, 2009; see also Rocca, Castagna, Mongini, Montemagni, Rasetti, et. al., 2009). Norton et. al. (2009) systematically manipulated dimensions of emotionality, distinctiveness of identity, and visual contrast by utilizing morphed images across tasks of emotion intensity discrimination, identity discrimination, and visual contrast detection. They found an overall deficit in SCZ patients for discriminating between emotional and neutral faces driven by a select impairment in their ability to discriminate fear, relative to healthy controls. No significant group difference was found for identity discrimination; however,

the fear discrimination deficits were predicted by performance on the contrast detection and facial identity tasks (Norton, McBain, Holt, Ongur, & Chen, 2009). Similarly, a delayed matching task manipulated what aspects of emotional faces were attended to, emotion or identity, and variably manipulated the unattended dimension, noting interference effects. That study found that SCZ patients were impaired on both tasks and had more difficulty selectively attending to one kind of facial information while ignoring the other, relative to healthy controls. However, the impairment was greatest for emotional stimuli. That is, performance was more drastically impaired for SCZ patients when the unattended dimension changed than for controls, and this was especially so when they had to match the same emotions in different faces. The authors concluded that patients have a general difficulty with processing facial information, but that this difficulty is particularly acute for facial emotion. While the literature overall thus remains inconclusive, these latter findings may indicate that impairment in emotion recognition, while certainly influenced by basic perceptual processing deficits, may constitute an additive or "extra" impairment in SCZ individuals.

It is worth noting that all of the studies of emotion perception deficits described thus far have examined the phenomenon in chronic, medicated SCZ patient populations, with the exception of the Kerr and Neale (1993) study which used an unmedicated sample. The impact of stage of illness on such deficits is relevant to consideration of whether such deficits reflect trait- versus state-like characteristics; however, few studies to date have taken a longitudinal approach. Pinkham et. al. (2007) compared early and chronic SCZ patients and found that both groups were equally impaired on emotion discrimination (matching) and identification (labeling) tasks. However, no such deficits were found in an "at-risk" for psychosis subgroup (Pinkham, Penn, Perkins, Graham, & Siegel, 2007). Addington and Addington (1998) assessed SCZ patients

longitudinally, during an episode of acute relapse resulting in hospitalization and 3 months later during a period of relative remission. They found that facial affect recognition deficits were stable across phase of illness and symptom severity. Also, although both positive and negative symptoms improved over that time, there was no improvement on any of the face processing tasks.

More longitudinal research will need to be completed before conclusions can be drawn regarding the stability of emotion perception deficits in SCZ. The relationship between such deficits and symptom severity may shed further light on the matter, yet findings to date are variable (Edwards, Jackson, & Pattison, 2002). In particular, positive symptoms are positively correlated with emotion recognition performance in some studies (e.g., Martin et. al., 2005, delusions only) and negatively correlated in others (e.g., Doop & Park, 2009; Rocca et. al., 2009). Negative symptoms are generally negatively correlated with emotion recognition performance (Norton et. al., 2009; Martin et. al., 2005), but a few studies show no correlation at all (e.g., Silver & Shlomo, 2001).

In contrast to the abundance of literature on emotion *perception* in SCZ, the role of disrupted emotion *regulation* mechanisms in the disorder is not yet well established. Much of the existing literature ties affect dysregulation to highly co-morbid substance use disorders (e.g., Mancini-Marie, Potvin, Fahim, Beauregard, Mensour, & Stip, 2006) and symptoms of paranoia (Williams, Das, Harris, Liddell, Brammer, et. al., 2004). More direct studies of emotion regulation utilize self-report methods to assess strategies utilized by SCZ patients and relate them to clinical symptoms such as difficulties self-identifying feelings (van der Meer, van't Wout, & Aleman, 2009) and clinical ratings of blunted affect (Henry, Rendell, Green, McDonald, & O'Donnell, 2008; see also Henry, Green, de Lucia, Restuccia, McDonald, O'Donnell, 2007). As

mood instability, perhaps the most direct indicator of emotional dysregulation, is a central diagnostic feature of BD, more research on this construct in SCZ is needed to ascertain whether elements of regulation are shared or distinct between the two disorders.

Overall, the deficits of the socio-emotional domain in SCZ revealed experimentally readily translate into observable functional difficulties for these individuals. For instance, Mueser et. al., (1996) found that poor general facial recognition ability was associated with reduced social competence. Hooker and Park (2002) found that performance on an affect matching task was negatively correlated with measures of communication and occupational dysfunction. More generally, clinical observers note that SCZ is characterized by constricted or inappropriate affect, avolition, suspiciousness, impaired social cognition and marked impairment in social and occupational functioning (Sayers, Curran, & Mueser, 1996; Green, Kern, Braff, & Mintz, 2000). Such impairments often manifest as problems attending school, maintaining work, parenting, and sustaining close relationships resulting in social withdrawal and isolation and occupational disability (Hafner et. al., 1994; Mueser & McGurk, 2004).

2.1b. Socio-Emotional Disruptions in Bipolar Disorder

Core features of BD include emotional reactivity, emotional instability, and mood dysregulation, along with distractibility, impulsivity, and irritability or poor frustration tolerance (e.g., Phillips, Drevets, Rauch, & Lane, 2003b). Such difficulties would seem to implicate disruptions along several points of the emotion-processing stream, including emotion perception and regulation, but empirical investigations examining these dimensions have been limited. In fact, a search for studies directly testing behavioral correlates of emotion regulation or dysregulation elicited few examples, perhaps owing to the difficulty of operationalizing the outward manifestation of this construct (cf., Phillips, Ladouceur, & Drevets, 2008; Green, Cahill,

& Malhi, 2007). Functional neuroimaging studies have begun to address this limitation, as will be discussed later. More work has been conducted on emotion perception impairments, although findings are likewise limited and inconclusive. For example, BD individuals appear to have intact perception and recognition of non-emotional faces across phases of illness (e.g., Bozikas, Tonia, Fokas, Karavatos, & Kosmidis, 2006; Getz, Shear, & Strakowski, 2003; Harmer, Grayson, & Goodwin, 2002; Venn, et. al., 2004); however, they show variable deficits in emotional facial perception.

More specifically, manic individuals have demonstrated impaired performance on facial emotion labeling tasks relative to healthy controls (Getz, et. al., 2003), with some studies also finding greater impairment in the specific recognition of fear and disgust, suggestive of a mood-congruent positive bias (Lembke & Ketter, 2002). Some of these findings indicate deficits selective to emotion labeling; when asked to discriminate between emotional faces in an emotion matching task, one sample of manic patients were indistinguishable from controls (Getz, et. al., 2003). In contrast, a generalized difficulty in discriminating low intensity facial expressions (i.e., decreased sensitivity) was seen in BD individuals in a depressive phase relative to controls, but without differences in overall accuracy. In fact, this group demonstrated higher accuracy for disgust faces compared with controls, possibly indicating a mood-congruent negative bias (Schaefer, Baumann, Rick, Luckenbaugh, & Zarate Jr., 2010). One study of remitted BD individuals indicated generalized impairment on an emotion matching task, uncorrelated with residual manic or depressive symptoms (Bozikas, et. al., 2006). In contrast, a study by Venn and colleagues found no specific deficits in emotion recognition, in terms of accuracy or sensitivity, in euthymic BD subjects. Although there was some evidence suggestive of a select deficit in fear recognition, this finding did not withstand further significance testing (Venn et. al., 2004).

Similarly, a study by Harmer and colleagues (2002) showed no impairment in discrimination of emotions at varying levels of intensity; rather, euthymic BD patients demonstrated selectively enhanced recognition for disgust faces (Harmer, Grayson, & Goodwin, 2002).

Clearly, a major point of distinction to be made between all of these studies is phase of illness and the effect of state- versus trait-dependent deficits on emotion processing. In particular, mood-congruent biases varying with respect to illness phase may indicate transient impairments of emotion processing rather than stable, trait-like difficulties as emotion processing deficits are viewed in SCZ (e.g., Lyon et. al., 1999; Murphy et. al., 1999; Lembke & Ketter, 2002; Schaefer, et. al., 2010; see also Van der Schot, Kahn, Ramsey, Nolen, & Vink, 2010). State-dependent impairments are important to consider, as these may be particularly amenable to treatment. However, establishing the nature of trait-like emotion processing deficits in BD, by focusing on performance in euthymic or remitted individuals, will be particularly informative in terms of the aims of the current study, toward developing a model of the neural phenotypic overlap and differentiation between BD and SCZ.

Although more research into the precise nature of socio-emotional deficits in BD is needed, that such deficits are present and debilitating is unmistakable. Indeed, in a manner similar to SCZ, impairments of emotion processing in BD translate into profound negative impacts on role functioning, interpersonal relationships, engagement in satisfying activities such as recreation or hobbies, and overall quality of life (Judd et. al., 2005). Furthermore, Dickerson and colleagues (2001) found that individuals with BD experience social impairments that are comparable in type and severity to those seen in SCZ patients. Specifically, BD patients were not significantly different from those with SCZ on measures of competence at daily living activities, participation in social activities, and frequency of family contact and social relations (Dickerson

et. al., 2001). Over the life span, psychosocial impairments associated with BD spectrum disorders are both chronic and disabling (Judd et. al., 2008), persisting even during periods of resolved clinical symptoms (Coryell et. al., 1993).

In summary, socio-emotional disruptions in SCZ and BD occur at the levels of emotion perception and emotion regulation. Separate lines of research have begun to investigate the neural correlates of disruptions of emotion perception in each disorder toward developing a model of the neural mechanisms underlying their pathogenesis (e.g., Phillips, et. al., 2003b). In contrast, there exists a paucity of empirical data on the neural basis of emotion regulation in psychiatric populations (Green & Mahli, 2007). This is surprising, given the obvious potential for a direct association between emotion regulatory mechanisms and affective disturbances, and represents a clear direction for future avenues of research. To that end, an understanding of the basic organization of these constructs, particularly basic and emotional face perception and controlled and incidental emotion regulation, as elucidated primarily by neuroscience investigations in healthy control individuals, would serve to strengthen interpretations to be made of the findings from such investigations in these clinical populations and establish rationale for use of a task drawn from this field for use in functional MRI studies directly comparing patients with SCZ, BD, and matched controls.

2.2. Basic Neural Organization of Socio-Emotional Processes

2.2.a. Face Processing

Identification of emotion from facial expressions is a primary example of emotion perception and requires broad visual perception abilities, including the basic ability to process faces. Human faces are essential for social interaction and communication and well equipped to

convey an abundance of information from person to person. It is no surprise, then, that face perception is one of the most highly developed of visual perceptual skills. Accordingly, a great deal of research has been dedicated to understanding how the brain processes faces.

Whether faces are processed differently from other types of stimuli and associated with a specialized neural system in the brain has been extensively investigated in cognitive psychology (e.g., Tanaka & Farah, 1993) and neuropsychology (e.g., Damasio, 1985; Damasio, Tranel, & Damasio, 1990; Malone, Morris, Kay, & Levin, 1982; Bornstein & Kidron, 1959; Beyn & Knyazeva, 1962). Numerous case studies of patient with focal brain legions point to bilateral regions of ventral occipitotemporal cortex as critical for facial recognition ability (Meadows, 1974; De Renzi, 1986; Sergent & Signoret, 1992). More recently, social cognitive neuroscience has provided greater detail about the putative neural system for faces.

Human imaging studies have reliably found that perception of faces is associated with activity in the lateral fusiform gyrus (LFG), which falls within the posterior temporal lobe portion of the lateral occipitotemporal gyrus, so much so that many have come to refer to this region as the fusiform face area or FFA (Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997; Halgren, Dale, Sereno, Tootell, Marinkovic, & Rosen, 1999). Other regions of visual extrastriate cortex that appear to be selective for faces include the inferior occipital gyrus (IOG), also known as the occipital face area (Rossion, Caldara, Seghier, Schuller, Lazeyras, & Mayer, 2003; Gauthier, Tarr, Moylan, Skudlarski, Gore, & Anderson, 2000; Halgren et. al., 1999; Sergent, Ohta, & MacDonald, 1992) as well as a region of the posterior superior temporal sulcus (pSTS; Engell & Haxby, 2007; Hooker, Paller, Gitelman, Parrish, Mesulam, & Reber, 2003; Haxby et. al., 2000). These regions of activation are usually bilateral but with a right hemispheric dominance.

Whether these regions act in a relatively independent but complementary manner to form a distributed neural network for face processing (e.g., Haxby et. al., 2000) or in a less discrete, more interactive fashion (e.g., Vuilleumier & Pourtois, 2007; Ganel et. al., 2005; Spangler, Shwarzer, Korell, & Maier-Karius, 2010), remains a subject of debate. Whether these regions are specialized for face processing per se also remains a matter of debate. Some researchers caution against making suppositions of strict functional subdivisions of brain regions, arguing instead for more generalized roles, such as of responsivity to visual expertise for LFG (e.g., Rhodes & McLean, 1990; Gauthier, et. al., 2000; Tarr & Gauthier, 2000; Chao, Martin, & Haxby, 1999), biological movement and observed intentional action for IOG (Bonda, Petrides, Ostry, & Evans, 1996; Saxe, Xiao, Kovacs, Perrett, & Kanwisher, 2004), and support of multiple cognitive operations for STS, depending on coactivation of task-dependent network connections (Hein & Knight, 2008). Overall, although advances have been made in our understanding of the neural underpinnings of face perception, more research is needed to elucidate the details of this complex system. What is clear, however, is that efficient processing of faces is reliant upon multiple interconnected brain regions acting in an orchestrated fashion.

Highlighting the importance of connectivity between neuronal regions in face processing, the model by Haxby, Hoffman, & Gobbini (2000) expands beyond a "core" system, comprised of the IOG, LFG, and pSTS and predominantly active for faces, to an "extended" system which contributes to face perception but is not exclusively involved in it. The extended system is modeled as brain regions involved in other 'downstream' operations activated by output of the core system. According to Haxby, "these brain regions, part of neural systems that perform other cognitive functions, become part of the face perception system when they act in concert with extrastriate face-responsive regions to facilitate recognition of different facial attributes" (Haxby

et. al., 2000). Similarly, Ishai and colleagues extend the distributed cortical network for faces to also include the amygdala, hippocampus, inferior frontal gyrus (IFG), and orbital frontal cortex (OFC; Ishai, Schmidt, & Boesiger, 2005). These other regions of the brain may be recruited depending on the type of face perception, to extract meaning from faces and process the significance of the information gleaned. For instance, perception of emotional facial expressions would activate the distributed neural system for emotion processing, including limbic regions such as the amygdala.

2.2.b. Perception of Emotional Facial Expressions

Similarly to primary face processing, the ability to display, recognize, and respond to facial expressions, or affect, are fundamental aspects of sociality in humans and critical for social information exchange (e.g., Ekman, 1993; Darwin, 1872). In fact, sensitivity to the emotional state of others is such that perception of emotional expressions can evoke a similar or related emotion in the perceiver. It is no surprise, then, that this type of face perception is reliably associated with neural activity in brain regions associated with emotion.

The neural network for emotional faces has generally been investigated in imaging studies that use comparisons of blank, expressionless, or neutral faces to faces displaying an expression of emotion. A recent meta-analysis of 100 neuroimaging studies utilizing emotional face stimuli found that several brain regions were consistently activated. In addition to face-responsive regions in extrastriate occipital cortex, the amygdala was the area of greatest overlap, followed by regions of inferior temporal cortex, medial prefrontal cortex (mPFC), and inferior frontal/orbitofrontal cortex (Sabatinelli et. al., 2011).

Amygdala activation has most often been associated with response to fearful but also neutral faces (e.g., Whalen et. al., 2001; Kesler-West et. al., 2001), regardless of spatial

frequency of the facial stimuli or location in the visual field (Morawetz, Baudewig, Treue, & Dechent, 2010). More generally, an abundance of literature points to the amygdala as playing a critical role in the automatic evaluation of both salient and ambiguous sensory inputs and then coordinating subsequent neurophysiological responses to these (LeDoux, 2000; Holland & Gallagher, 1999; Posner, 2001) possibly by biasing cognition toward perceived stimuli with potential emotional and social significance (Adolphs, 2003; Vuilleumier & Pourtois, 2006). For example, Critchley et. al. (2000) compared activation to fearful and angry faces when explicitly (judging expression task) versus implicitly (judge facial gender task) attended to, and found that implicit processing involved greater amygdala activation. Similarly, Anderson and colleagues (2003) found that directing attention away from disgust and fear faces modulated regions involved in disgust (i.e., insula) but not amygdala; rather, amygdala activation increased. These findings suggest that when such stimuli are not attended to, amygdala processing becomes more diffuse to threat in general or attuned to the task of resolving ambiguity.

Selective involvement of other brain regions for emotions in a category specific manner has also been investigated with varying degrees of consistency. Generally, findings implicate a network of predominantly anterior limbic regions including the amygdala, ventral striatum, hippocampus, and anterior insula (Vytal & Hamann, 2010; Kesler-West et. al., 2001; Sprengelmeyer, et. al., 1998; Phillips, 2006). In line with elements of the face processing model described above (e.g., Haxby et. al., 2000; Hein & Knight, 2008), Peelen et. al., (2010) found that mPFC and left STS activation was associated with presentation of five different emotions (fear, anger, disgust, happiness, sadness) in category-specific patterns of intensity but independent of modality of sensory input (i.e., facial expressions, body movements, or vocal intonations) or emotional intensity of the stimuli. They suggested that these "higher-level" brain

areas (also implicated in mental state attribution and theory of mind) represent emotions at an integrated, abstract, supramodal level and thus play a key role in understanding and categorizing others' emotional mental states.

2.2.c. Emotion Regulation

Consideration of the interplay between cortical and subcortical brain regions in emotion processing highlights those mechanisms which likely subserve emotion regulation. Emotion regulation, another core element of the emotion processing stream, most often refers to the conscious and deliberate modulation of our experience of and behavioral response to arousing, self-significant stimuli. Often, this is achieved by means of intentional cognitive strategies, including reappraisal of the meaning of an emotional event or effortful control of attention to emotionally evocative stimuli (e.g., Ochsner & Gross, 2005; 2008). Neuroimaging studies of intentional emotion regulation generally find recruitment of prefrontal regions, especially dlPFC, vlPFC, dmPFC, and dACC, with a corresponding decrease in activation of limbic structures, especially amygdala, as well as mOFC (e.g., Ochsner, Bunge, Gross, & Gabrieli, 2002; Kim & Hamann, 2001; Phillips et. al., 2003a; Green & Malhi, 2006). In this way, while attention to emotional stimuli can be biased by "preattentive" processes in a "bottom-up" fashion, response to emotional stimuli can also be modulated by "top-down" conscious control operations toward, for example, task performance (LeDoux, 2000; Stel & Knippenberg, 2008). A burgeoning area of inquiry is the more automatic forms of emotion regulation, which may occur incidentally and possibly outside of conscious awareness (Berkman & Lieberman, 2009).

Importantly, tasks that assess incidental emotion regulation may reflect more of an individual's "tendency" to engage in emotion regulation rather than their "capacity" to do so (Berkman & Lieberman 2009; Gross & John, 2003). While such tasks do not explicitly instruct

an individual to regulate emotional responses, they are nevertheless associated with patterns of neural activity similar to those that consistently index overt emotion regulation paradigms. Incidental emotion regulation mechanisms are of particular interest to the current study since BD individuals may have intact capacity for emotion regulation strategies but tend not to utilize them. In fact, Phillips and colleagues (2008) posit that understanding the neural organization of incidental emotion regulation is critical to understanding the pathophysiology of BD (Phillips, Ladouceur, & Drevets, 2008).

Examples of paradigms which may tap automatic or incidental emotion regulation processes include those in which context alters affective response outside of awareness (e.g., Hare, Tottenham, Davidson, Glover, & Casey, 2005) and those that manipulate attention to emotional stimuli in a task irrelevant manner, especially in tasks which employ language processing (Hariri et. al., 2000) and with high cognitive load (Pessoa, Padmala, & Morland, 2005). These two latter aspects of incidental emotion regulation task paradigms warrant further discussion in relation to the aims of the current study.

First, there is evidence to suggest that tasks engaging the interplay between emotion and language may be particularly suited to explicate the nature of incidental emotion regulation systems. Hariri, et. al., (2000) introduced a paradigm in which participants were asked to selectively judge faces' emotional characteristics by choosing an affective word label (linguistic processing) or choose a face with a matching emotional expression (perceptual processing). They found that linguistic processing of the emotional aspects of an emotional image produced less amygdala activity with a corresponding increase in vlPFC activity than perceptual processing of the emotional aspects of the same image. In a follow-up, Lieberman, et. al., (2007) introduced additional control conditions, gender labeling and gender matching of the same emotional faces,

to demonstrate that this inverse pattern of activation is exclusive to affect labeling. Additionally, they found that attenuation of the amygdala via activation of the vlPFC (specifically in the right hemisphere) was mediated by mPFC. Studies of affect labeling in patient groups demonstrate that this task is sensitive to differential recruitment of neural networks in the incidental processing of emotional faces, even when accompanied by minimal behavioral differences, in disorders impacting social functioning such as autism (e.g., Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004).

Second, the study by Pessoa and colleagues (2005) found that manipulations in attention reduce the processing of unattended emotional stimuli (i.e., reduce amygdala activity) only when the task is of sufficient cognitive demand to largely consume processing capacity. These results are in line with the idea that processing of unattended items, even highly salient emotional items, is limited by attentional capacity (Lavie, 1995; Yates, Ashwin, & Fox, 2010). The implication is then, that attention will be unintentionally and automatically biased *toward* task irrelevent emotional stimuli (with increased amygdala activity) as long as attentional capacity has not been reached. This notion fits well with the idea of differential modulation of amygdala depending on "top-down" versus "bottom-up" influences. A second important implication is that evidence of downward modulation of limbic regions via increased recruitment of frontal regions during incidental emotion regulation tasks would not only necessitate intact fronto-limbic structural and functional connectivity, but also that participants be fully engaged in the cognitively demanding task.

Based on the foregoing, select deficits of face processing, emotion expression perception, and incidental emotion regulation would not be surprising if any of the core systems involved are dysfunctional and/or if connectivity between networks is impaired. Although existing literature is

sparse for either patient group, functional neuroimaging has increasingly been utilized to probe these deficits in SCZ and BD.

2.3. Neural Activation Abnormalities of the Socio-Emotional Domain in Severe Mental Illness

2.3.a. Neuroimaging evidence of emotion perception disruption in SCZ

fMRI studies in individuals with SCZ indicate a pattern of decreased or absent activation of subcortical regions in response to facial expressions of fear and other emotions (e.g., Gur et. al., 2007; Kosaka et. al., 2002; Hempel et. al., 2003; Phillips et. al., 1999). For example, Williams and colleagues (2007) found that facial expressions of fear, anger, and disgust elicited decreased activity of the amygdala, insula, and ACC in SCZ compared to healthy controls. Similarly, Taylor and colleagues (2005) found reduced fMRI activity in the amygdala and ventral striatum in response to both positive and aversive stimuli in patients with schizophrenia relative to controls (Taylor, Phan, Britton, & Liberzon, 2005). These findings appear to be consistent across tasks of varying degrees of difficulty and focus of attention to different aspects of the emotional faces (Kohler & Brennan, 2004). Gur et. al., (2002) designed a task in which faces displaying varying degrees of emotional intensity across five emotions (happiness, sadness, anger, fear, disgust) plus neutral faces were judged according to valence (positive or negative) or age (younger or older than 30). Patients with SCZ showed reduced activation of the left amygdala and bilateral hippocampus during the valence discrimination task, although their performance on the task was not impaired (Gur, et. al., 2002). Such reduced recruitment of neural circuitry involved in emotion perception on a task patients successfully completed would seem to remove confounds of task difficulty, suggestive of a fundamental deficit in processing

emotional information (although this would likely manifest as impaired performance on more difficult tasks).

Other researchers have utilized more subtle aspects of emotional face perception to investigate possible neural mechanisms underlying SCZ symptoms such as paranoia. Habel and colleagues (2010) had SCZ patients and healthy controls respond by pressing one button when a target emotion was presented and another when a non-target emotion or neutral face was presented. They found that patients were able to correctly identify target emotions; however, patients tended to judge neutral faces as emotional more than controls and, more specifically, to misinterpret neutral faces as angry or fearful. This tendency was correlated with negative symptom severity. Furthermore, the patients showed a diffuse and complex pattern of differential activation patterns in an emotion category specific manner, which the authors summarized as a general overactivation of prefrontal and midline ventral regions in response to non-emotional information, perhaps as a result of misattributing emotional meaning to neutral stimuli. In contrast, general hypoactivation of the regions known to be involved in basic face processing was also observed (Habel et. al., 2010). Furthermore, a recent study by Rauch and colleagues (2010) found hyper-responsivity to negative and positive facial expressions in SCZ patients when processing emotion faces on an automatic or sub-conscious level. In that study, brief (i.e., suboptimal) presentation of emotional faces immediately preceded longer presentations of neutral faces, to prime judgments about the emotionality of neutral faces. While the behavioral priming effect was equivalent between groups, the SCZ group showed greater bilateral amygdala activation to masked emotional faces (sad and happy) compared to masked neutral faces, whereas controls showed greater hippocampal activation to masked happy faces. Those authors note that the discrepant finding may be due to previous studies (e.g., Gur et. al., 2002) using

neutral faces as the baseline comparison condition, which could result in underestimation of the general response to emotional faces (Rauch et. al., 2010). However, another possibility is that separately examining incidental versus controlled emotional information processing in SCZ may reveal dissociable abnormalities in both processing modes. In this way, the evident hypoactivation of various subcortical regions during explicit face processing could reflect the generalized face processing deficit described earlier. On the other hand, hyperactivation of these regions during implicit processing may reflect hyper-vigilance to ambiguity that is otherwise masked during explicit tasks. A recent meta-analysis by Li et. al., (2010) found that SCZ individuals generally exhibit reduced activation of basic face processing regions, bilateral amygdala and parahippocampal gyrus, but enhanced activation of left insula. Further, they found that a relative failure to recruit amygdala occurred regardless of whether the processing of emotional information was explicit or implicit, while reduced activity in other face regions (e.g., fusiform gyrus) occurred exclusively during explicit face processing, not implicit. Notably, the recent study by Rauch and colleagues (2010) was not included in the meta-analysis.

2.3.b. Neuroimaging evidence of emotion perception disruption in BD

A small number of neuroimaging studies have investigated emotion perception in BD during various phases of illness (i.e., during manic, depressive, and euthymic states). Specifically, manic BD individuals showed decreased bilateral amygdala and subgenual ACC activity, and increased posterior cingulate and posterior insula activity, to sad but not happy facial expressions, with a corresponding attenuation in subjective intensity ratings of sad expressions (Lennox, Jacob, Calder, Lupson, & Bullmore, 2004). In contrast, depressed BD individuals showed abnormally elevated left amygdala response to mildly sad and neutral faces during an emotion labeling paradigm relative to depressed individuals diagnosed with recurrent

major depression, remitted BD patients and healthy controls. Those individuals were also less accurate than healthy controls at labeling happy faces (Almeida, Versace, Hassel, Kupfer, & Phillips, 2010). Such findings could reflect state-level influences of mood-congruent processing biases.

An inverse pattern of decreased dlPFC activity and subcortical and mPFC overactivity is beginning to emerge in a collection of studies in euthymic BD individuals utilizing an indirect emotion perception task in which emotional faces of varying intensity are judged solely on the basis of gender. Utilizing this paradigm, Surguladze and colleagues (2010) observed increased activation in mPFC and left putamen in response to all happy and fearful faces and increased activation in left amygdala to intensively happy faces in remitted BD patients relative to controls. Similarly, Hassel and colleagues (2008) found increased left striatal activity in response to happy faces, decreased right dlPFC activity in response to happy and neutral faces, and decreased left dlPFC in response to neutral and fearful faces in euthymic BD patients relative to controls. However, no difference in amygdala activity in response to happy, fearful, or neutral faces was found between the groups. Similar findings of increased subcortical activation were described by Lawrence et. al., (2004); however, they also found increased vlPFC activity in response to faces of intense fear, mild happiness, and mild and intense sadness relative to controls. Importantly, that group's findings are not unlike those utilizing more direct affect recognition tasks. For example, Yurgelun-Todd and colleagues (2000) found reduced dlPFC activation and increased amygdala activity in stable BD patients relative to controls when presented with fearful but not happy expressions. Their findings were not compared relevant to current symptom severity in the patient group (Yurgelun-Todd, Gruber, Kanayama, Killgore, Baird, & Young, 2000). Of course,

only tentative conclusions may be drawn from such a limited number of studies utilizing so few task paradigms, highlighting the need for more research in this area.

2.3.c. Neuroimaging evidence of incidental emotion regulation disruption in SCZ

A review of the literature found no neuroimaging studies explicitly examining intentional emotion regulation in SCZ patients. However, one study examined the neural correlates of cognitive reappraisal in a group of individuals with low versus high scores on a psychosis proneness (PP) scale (Modinos, Ormel, & Aleman, 2010). High PP individuals had greater prefrontal activation than the low PP group, and amygdala activation was decreased through reappraisal only in the low PP group. Furthermore, functional connectivity analysis revealed that high PP individuals had less prefrontal-amygdala coupling during successful cognitive reappraisal (Modinos, Ormel, & Aleman, 2010). Those authors suggest that emotion regulation difficulties may thus contribute to psychosis vulnerability. Such findings are intriguing and highlight the need for more research in this area.

Similarly, no studies have utilized incidental emotion regulation paradigms, per se, in this population. However, as pointed out by Berkman and Lieberman (2009), some studies may engage incidental emotion regulation mechanisms without that express intent. For example, one study sought to engage amygdala-prefrontal networks in SCZ patients and healthy controls via an incidental fear response (Williams, et. al., 2004). They presented participants with fearful and neutral faces and asked them to judge only the gender of the faces. Paranoid SCZ patients demonstrated decreased amygdala, mPFC, and ACC activity with high arousal in response to fearful faces relative to healthy controls (Williams, et. al., 2004). In addition, a recent group of studies examined effects of interactions between cognition (performance on a verbal n-back working memory test) and emotion (simultaneously inducing negative affect via foul odors) on

limbic-prefrontal networks in adult (Habel et. al., 2010) and adolescent-onset (Pauly et. al., 2008) SCZ patients and individuals clinically at risk for psychosis (CHR; Pauly, et. al., 2010). Behaviorally, those studies found that negative affect stimulation interfered with task performance similarly in all groups. However, the interaction between emotion and cognition generated altered patterns of activation in patient groups in the thalamocortical network. Specifically, adult SCZ patients, relative to controls, showed decreased activation in right superior frontal cortex and dACC and increased activation in left middle frontal gyrus and medial left orbitofrontal gyrus (Habel et. al., 2010). In the adolescent-onset group, decreased activation was found in left thalamus, right angular gyrus, left superior temporal gyrus, inferior occipital gyrus, and posterior cingulate gyrus extending to the precuneus compared to controls. Finally, decreased activation was found in right STG and thalamus for the CHR group relative to controls. None of these studies found between-group differences in activation of the amygdala for these interactions. All together, these findings seem to indicate a mixed pattern of diffuse alterations in SCZ individuals along cortical-subcortical networks with a clear pattern yet to emerge. Additional studies directly assessing the nature of disruptions in mechanisms of cortical (cognitive) influence on subcortical (emotional) regions in SCZ need to be conducted before such findings can be organized into a coherent framework. Utilizing a task that has been shown to activate such a cross-regional brain network reliably in healthy controls may be particularly informative in this regard.

Other, related domains of research may also inform the present inquiry. For example, there is an extensive body of literature characterizing disruptions of neural connectivity in SCZ as relevant to the pathophysiology of the disorder, which may be functionally based (e.g., Friston & Firth, 2005), anatomically driven (e.g., Bullmore, Frangou, & Murray, 1997), or some

combination of the two (for a review, see Karlsgodt, et. al., 2008). Such disruptions would likely impact any neurocognitive function that relies upon distributed neural systems dependent on both short- and long-range connectivity, including both incidental and controlled emotion regulation.

2.3.d. Neuroimaging evidence of incidental emotion regulation disruption in BD

In line with our understanding of the basic neural system involved in emotion regulation, several researchers posit that dysfunctional neural circuitry in BD manifests as an imbalance between cortical and subcortical activity, whereby reduced dorsal prefrontal performance is associated with the disinhibition of subcortical structures, including amygdala, striatum, and thalamus (Sheline, 2003; Strakowski et. al., 2004; Phillips et. al., 2008). Although few studies have explicitly examined the neural mechanisms of emotion dysregulation in BD, findings are promising in those that have. For example, Foland and colleagues (2008) utilized a paradigm similar to the incidental emotion regulation tasks described above, comparing conditions of emotion labeling versus emotion matching in manic BD patients. They found that patients did not recruit vlPFC to modulate amygdala relative to controls, suggesting that reductions in inhibitory frontal activity may lead to increased reactivity of amygdala (Foland, Altshuler, Bookheimer, Eisenberger, Townsend, & Thompson, 2008). Similarly, a study employing an affective go/no-go paradigm in manic individuals found decreased vmPFC activation during semantic task versus orthographic go/no-go task performance, but increased vlPFC activation to emotional versus neutral targets, and elevated ventral and medial PFC responses to emotional distractors (Elliott et. al., 2004).

2.3.e. Neuroimaging Evidence of Anatomical Deficits in SCZ and BD

Although extensive review of the literature on neuroanatomical abnormalities in SCZ and BD is beyond the scope of this paper, a brief mention of findings in regions particularly implicated in emotion processing is warranted. Extensive research has established that individuals with SCZ exhibit a range of volume differences in the brain compared to healthy controls, such as reduced cortical, amygdala, hippocampal, and thalamic volumes and increased sulcal and ventricular volumes (e.g., Andreasen et. al., 1994; Byne et. al., 2002; Pfefferbaum & Marsh, 1995). Frontal and temporal cortical volumes may be reduced to a relatively greater degree than posterior cortical volumes (Cannon et. al., 1998). There is also evidence for impaired connectivity between these regions (Karlsgodt et. al., 2008), and disrupted connectivity has been associated with negative symptom severity (e.g., Szeszko, Robinson, Ashtari et. al., 2007). Although not as thoroughly studied in BD, some anatomical findings in this group may also relate to emotion difficulties primary to the disorder. While individuals with BD do not appear to demonstrate generalized cortical gray matter deficits as individuals with SCZ do, reduced cortical volume in circumscribed regions of prefrontal cortex and select amygdalar enlargement have been observed (Beyer & Krishnan, 2002; Altshuler et. al., 1998). The functional significance of these changes is not yet well understood.

2.3.f. Direct Comparisons of SCZ and BD on Emotion Processing Tasks

While many aspects of emotion processing abnormalities, corresponding functional deficits, and abnormalities in associated neural systems evident in SCZ and BD are strikingly similar, others may be quite distinct. Until recently, few studies directly compared the two disorders to quantify these qualitative similarities and differences (cf., Altshuler et. al., 1998), and even fewer attempted to make direct comparisons on socio-emotional processing dimensions specifically. One early study utilized a remitted BD sample as a psychiatric control group in a

behavioral study of emotion perception in SCZ (Addington & Addington, 1998). This study found that the SCZ group demonstrated lower performance than the BD group across facial emotion discrimination (matching) and identification (labeling) and non-emotional facial identity recognition tasks. Furthermore, BD individuals were impaired relative to controls only on the facial emotion discrimination (matching) task, and their performance fell in between that of SCZ patients and controls. In another behavioral study, Bellack, Blanchard, and Muser (1996) directly compared SCZ and BD patients on a test of facial affect recognition and found that the two groups did not differ, although they were different on non-emotional perceptual tasks.

More recently, researchers have begun to investigate neuroanatomy and neural systems associated with functional deficits in the emotion processing domain by direct comparison of the two disorders. In a structural MRI study, Mahon et. al. (2012), found smaller amygdala volumes in patients with SCZ compared to patients with psychotic BD. Morris and colleagues (2012) examined SCZ, BD, and healthy controls during fMRI on a task of deliberate emotion regulation and found that patterns of cortico-limbic activation unique to SCZ and BD distinguished the two groups, especially during attempts to down-regulate negative affect. Finally, a few studies have explicitly tested resting-state functional connectivity (rsFC) within neural systems implicated in the two disorders. Liu et. al. (2013) examined rsFC between PFC and amygdala in SCZ and BD groups, and found significantly decreased connectivity in both groups relative to controls, but with dorsal (for SCZ) versus ventral (for BD) PFC differentiation in PFC-amygdala neural system abnormalities. Similarly, Chai et. al. (2011) found similar decoupling of mPFC and dlPFC in BD and SCZ; however, mPFC and insula/vlPFC were positively correlated in BD patients whereas no correlation or inverse correlation between these regions was observed in SCZ patients. Taken together, findings are mixed but tend to lend more support for

differentiation between the two disorders in terms of underlying neuroanatomical and neurofunctional differences relative to controls.

While such results are intriguing, more work is clearly needed. *Importantly, no prior study has compared SCZ and BD patients directly on emotion perception or incidental emotion regulation paradigms while undergoing functional imaging*. Questions of nosology require direct, within study comparisons across both behavioral and neurophysiological levels of analysis across a broad range of processes within multiple cognitive and affective domains. In addition, the prior studies of direct diagnostic group comparison cited above all suffer from relatively small sample sizes (ranging from 12-18 subjects per group for functional imaging studies), thus increasing risk of false positive results and potential for inadequate power to detect effects. I aimed to address these limitations in my dissertation research.

III. RESEARCH PLAN

We utilized the affective labeling paradigm introduced by Hariri et. al., (2000) and modified by Lieberman et. al., (2007) during fMRI to examine the neural systems involved in deficits of emotion perception, specifically of emotional facial expressions, and incidental emotion regulation. This task has several advantages, in that it is able to tap both explicit and more implicit perception of emotion and implicit or incidental emotion regulation mechanisms. This is accomplished by manipulating attention toward or away from emotional aspects of faces and in a manner that does and does not involve linguistic processing. In this way, this task is sensitive to deficits in basic face processing, impairments in emotion perception, and disruptions in regional neural activity required for successful incidental emotion regulation.

To that end, we examined both behavioral and neural correlates of these aspects of emotion processing with the goal of establishing the nature of phenotypic overlap and differentiation between the patient groups relative to controls, as well as specific emotion processing deficits within (patient) groups. In terms of behavioral data, task performance was examined for between and within group effects of task condition on Accuracy (Acc) and Reaction Time (RT). Between groups analyses utilized mixed models analyses of variance with repeated measures (separate for Acc and RT). Planned comparisons were used to parse out the specific nature of significant omnibus differences between groups and details of within group differences. All analyses covaried for age and gender.

In regards to the neuroimaging data, we performed whole-brain voxel-wise analysis (cluster-threshold of $p < .05$) to examine differences between groups in putative face processing regions (i.e., IOG, LFG, pSTS), regions implicated in emotion processing (i.e., amygdala, mPFC, IFG, and OFC), and regions thought to be involved in incidental emotion regulation (i.e., vlPFC, dmPFC, and dACC). Additionally, neural networks reliant on connectivity and coordinated action between these regions were examined via functional connectivity analysis. Finally, correlations between behavioral deficits and symptom severity were measured to inform relevant clinical considerations. Exploratory analyses were further performed to examine relationships between neural activity in discrete regions of interest (i.e., amygdala, a region critical for emotion processing, vlPFC, a region instrumental in incidental emotion regulation, and dlPFC, a region integral to efficient task performance), behavioral deficits, and symptoms to better characterize the impact of brain activity on functional outcomes.

IV. HYPOTHESES

4.1. Rationale

If emotion processing deficits at the level of facial expression perception and incidental emotion regulation represent a phenotypic dimension that unifies SCZ and BD, then both groups will differ from controls but not each other on performance during tasks of facial expression recognition (i.e., *affect-match* and *affect-label* conditions*),* corresponding neural activity in response to emotion recognition tasks (i.e., during the *affect-match* condition), and neural activity reflecting incidental emotion regulation ability (i.e., during the *affect-label* condition). If, however, emotion processing deficits expose differential features of these disorders, then SCZ and BD patients will differ from each other and controls on select behavioral indices of emotion perception and corresponding neural activation patterns reflective of emotion perception and incidental emotion regulation.

Although no prior study has performed such a direct comparison on imaging measures, based on the patterns of differences between each patient group and controls in prior work, we expected the following:

4.2. Hypotheses

1. *Behavioral Data*
    a. Poor performance will be shared by SCZ and BD groups during tasks of facial affect recognition conditions (i.e., *affect-match* and *affect-label* conditions*)* relative to healthy controls.
    b. Since emotion recognition deficits in SCZ will be accompanied by additional deficits in basic face perception, the evident impairment will be relatively greater in SCZ than BD, particularly in the match condition which involves an additional cognitive load in terms of feature comparisons across images.

2. *Imaging Data – corresponding neural activity differences*
    a. Reduced amygdala activation in both SCZ and BD groups relative to controls during emotion recognition (i.e., *affect-match* and *affect-label* conditions).
    b. Reduced amygdala modulation by (i.e., negative connectivity with) vlPFC in both SCZ and BD groups during affective labeling.
    c. Reduced activation in the SCZ group relative to both BD patients and controls in regions associated with basic face perception during *Match* conditions
3. Task performance in the SCZ group will be negatively correlated with negative and positive symptoms.
4. Task performance in the BD group will reflect trait- rather than state-like deficits in emotion perception among euthymic individuals that is uncorrelated with residual symptoms of mania or depression.

V. METHODS

Data for this study were collected at the Karolinska Institute in Stockholm, Sweden. The study protocol was reviewed and approved by the Institutional Review Boards (IRB) of the University of California, Los Angeles and the regional ethical review board at Karolinska Institute. All individuals signed IRB-approved informed-consent forms prior to participation.

5.1. Subjects

To identify a participant pool from which to draw eligible subjects, medical records data from the National Board of Health and Welfare were merged with the Swedish Twin Registry to yield individuals who were members of twinships and who had a hospital discharge diagnosis of SCZ or BD or who had no personal history of psychiatric hospitalization (Lichtenstein, et. al.,

2008). This process yielded 562 potential patients: 257 male and 305 female, ranging in age from 25 to 65. Potential control subjects, matched to each patient by age and sex, were also recruited from the participant pool.

5.2. Procedures

5.2.a. Clinical evaluation: Each participant was interviewed by an examiner blind to diagnostic history using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P; First, Spitzer, Gibbon, and Williams, 2002) and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First, Gibbon, Spitzer, Williams, & Benjamin, 1997). All subjects were also rated using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960), Young Mania Rating Scale (YMRS; Young et. al., 1978), and the NAPLS Social and Role Functioning Scales (Cornblatt et. al., 2005). For each subject, a detailed case report summarizing clinical, social, occupational and medical history was generated and a consensus on diagnostic status reached after review by principal Karolinska Institute researchers.

5.2.b. Participation criteria: Eligibility for inclusion as a patient was a consensus diagnosis of SCZ, schizoaffective disorder, schizophreniform disorder, or bipolar I disorder. All patients were clinically stable, receiving medication and/or in a period of remission or euthymic. No modification to existing medication regimes was made in relation to participation in the study. Exclusion criteria for all participants was mental retardation, history of substance use disorder within 6 months of the screening interview, inability to read or comprehend spoken and written Swedish, and not between the ages of 25 and 65 years at the time of evaluation. No healthy

control participants received a consensus diagnosis of any psychotic disorder, bipolar spectrum disorder, obsessive-compulsive disorder, panic disorder, attention-deficit hyperactivity disorder, or conduct disorder. Participants were excluded for task accuracy within 3 standard deviations of chance performance or insurmountable imaging artifacts. One potential participant with BD and one with SCZ were excluded for behavioral performance; two potential BD participants and one potential control were excluded for imaging artifacts.

Total final number of participants was 143 individuals: 41 with SCZ, 38 with BD, and 64 control participants. Demographic and clinical characteristics of the sample are shown in Table 1. There were no differences between groups in terms of age, sex, handedness, or years of education. As expected, significant group differences were observed in medication status between patients and controls, with most SCZ and BD individuals on antipsychotic and/or mood stabilizing medication, as well as in symptom ratings, such that SCZ and BD patients had elevated scores relative to controls.

5.2.c. Task Design: Participants completed an affective labeling paradigm modeled after the task utilized by Lieberman et. al., (2007) and Hariri et. al., (2000). During the task, participants view target faces displaying emotional expressions or target shapes above simultaneously presented response choices, varying depending on the task, across two runs in a block design. Each run comprises five blocks (conditions), consisting of ten trials pseudo-randomly selected from a pool of trials. Each condition appears once per run in a counterbalanced order.

During the *affect-label* condition, participants choose the word label that best describes the target (i.e., “scared,” “angry,” “neutral,” “happy,” or “surprised”) from a pair of words shown at the bottom of the screen. During the *gender-label* condition, participants are to choose the gender-appropriate name from a pair of names shown at the bottom of the screen. During the

affect-match condition, participants choose the face from the pair at the bottom of the screen that expresses the same emotion as the target. During the *gender-match* condition, participants choose the face from the pair at the bottom of the screen that is the same gender as the target face. Finally, during the *shape-match* condition, subjects choose the shape from the pair of shapes at the bottom of the screen that is the same as the target shape.

Each face condition is comprised of four fearful faces, four angry faces, one surprised face, and one happy face as the target face. Half of the target faces in each condition are male and half are female. The face stimuli were selected from a standardized set of images (Tottenham, Borscheid, Ellersten, Markus, & Nelson, 2002). For the *affect-label* and *gender-label* conditions, word labels were translated into Swedish by study collaborators in Sweden; the task translation was validated through a pilot study to ensure commonality and frequency of use of names chosen were comparable to the English version. In addition, an effort was made to match the first letter and total number of letters in the gender-appropriate name with the correct emotional label. For example, "ROLF" was matched with "RÄDD" (analogous to "Samuel" matched to "Scared" in English). All stimuli are presented visually through goggles on a screen with 800x600 resolution via E-prime® stimulus presentations software E-Prime (Psychology Software Tools, Pittsburgh, PA).

A 10-second (s) fixation block is presented at a) the beginning of each scan, b) at the end of each scan, and c) between each task block. In addition, a 2.5s instruction slide is displayed before each task block begins, to inform the subject of the condition that will be displayed. Stimuli/trials are presented for 5s each. Subjects' responses are recorded through a hand-held fiber-optic response box connected to a computer, allowing for both button presses and reaction time to be recorded. Subjects are told to respond as quickly and accurately as possible. The

stimuli remain on the screen for the entire 5s trial. The total scan time for both runs of the task is 10 min 45 seconds.

Prior to scanning, participants completed a training session via E-prime® on a computer outside the scanner. First, instructions for each condition are displayed and participants are allowed to ask clarifying questions until the administrator is confident that the subject fully understands the task. Then, brief practice trials for each condition are completed with performance feedback provided ("correct," "incorrect," or "no response detected"). The training phase takes approximately four minutes to complete.

5.2.d. Imaging Acquisition: Data were acquired on a 1.5 Tesla GE (Milwaukee, WI) scanner equipped with a fast gradient system for echo-planar imaging with a standard radiofrequency (RF) head coil. For each subject, a high resolution structural T2-weighted image was acquired for anatomical registration [spin-echo; AC-PC aligned; repetition time (TR) = 4000ms; echo time (TE) = 82 ms; 25 axial slices; 4mm thickness; matrix size = 128x128] as well as two T2*-weighted blood oxygen level-dependent (BOLD) gradient echo planar imaging (EPI) sequences (TR = 2500 ms; TE = 40ms; flip angle = 90°; 25 interleaved slices, 3.5mm thickness; voxel size = 3.44 x 3.44 x 4.5; matrix = 64 x 64). 129 volumes are collected during each functional scan.

5.3. Statistical Analysis

5.3.a. Behavioral Data: Mixed models analyses of variance with repeated measures were conducted to examine between and within group effects of task condition on Accuracy (Acc) and Reaction Time (RT). A multivariate approach was used to guard against type I errors, and simple effects were only examined when multivariate effects were significant. To account for the clustered nature of the twin data (among control subjects) and correlation among repeated

effects, subjects were treated as individuals nested within pairs, and the data were modeled with an unstructured variance-covariance matrix form, allowing for unique variance within each group and covariance within each twin pair.

Analyses were conducted separately for Acc and RT. Age and sex were entered into the models as covariates. In the presence of a group x condition interaction, simple effect analyses were performed using a mixed model univariate approach. Significant group effects were evaluated with post-hoc t-tests. All analyses measured significance at the .05 level (two-tailed, unless otherwise noted). Statistical analyses of behavioral data were conducted using IBM SPSS Statistics for Windows Version 20.0 (SPSS; Armonk, NY: IBM Corp).

5.3.b. Image Preprocessing and Registration: Functional imaging data were preprocessed and analyzed using FSL software tools (FMRIB's Software Library v4.1.9; Analysis Group, Oxford, UK). Data were spatially smoothed using a 5-mm full-width-half-maximum Gaussian kernel and temporally filtered using a 100s cut-off highpass filter. Images were skull stripped using BET (Brain Extraction Tool; Smith, 2002). Motion correction was done using MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) with resulting movement parameters modeled as nuisance covariates. Translational movement parameters did not exceed 2 mm in any direction; movements greater than 1 mm were flagged for manual correction. Problematic motion did not differ by group ($x^2(2, N=143)=3.23, p=.20$).

A three-step registration procedure utilized FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson et. al., 2002). BOLD EPI images were first registered to individual T2 structural images via 6-parameter rigid-body transformation, then to a study-specific standard brain via 12-parameter linear affine transformation. Individual subjects with missing or unusable T2 images were registered to a group-specific common brain in the initial step. Statistical analyses of

functional data were performed in native space, with the statistical maps normalized to study-specific standard space prior to higher-level analyses. Group level results were finally transformed to Montreal Neurological Institute (MNI) standard space via affine transformation to allow for reporting of universal coordinates and cross-study comparisons.

The three-step registration procedure was chosen due to the fact that the brains of patients with severe psychopathology may be morphologically different from those of control participants and subjects comprising standard space templates. Therefore, a group-averaged template or standard brain was created out of subjects included in the analyses, rather than using a pre-existing standard space image for group-level registration. This study-specific standard brain served to minimize the distortion of the functional data during spatial normalization and avoid creating spurious group differences due to relatively greater distortion in the patient groups relative to the control group (see Karlsgodt, Glahn, van Erp, Therman, Huttunen, et. al., 2007). This was accomplished via an iterative averaging process using FLIRT (FMRIB's Linear Image Registration Tool v5.5) and the fslmaths tool.

5.3.c. fMRI Analysis: Analysis of functional data was performed using a multi-stage general linear model approach with FEAT (FMRI Expert Analysis Tool v5.98). At the first-level, event modeling was performed separately for each run using a canonical double-gamma hemodynamic response function (HRF). Each condition (*affect-label, gender-label, affect-match, gender-match, shape-match*) was modeled as an explanatory variable (EV). Incorrect trials and trial time remaining after a participant made a response were modeled out as nuisance variables. Null events, including six 10-second fixation blocks, were not explicitly modeled, constituting an implicit baseline. The two runs for each participant were then averaged together in a higher-level fixed effects model. The group-level analysis was done using the FMRIB's Local Analysis of

Mixed Effects (FLAME) stage 1 module in FSL (Beckmann, et. al., 2003). Voxel-wise BOLD signal analysis was used to examine contrasts of parameter estimates. Unless otherwise noted, only clusters exceeding a height threshold of $Z > 2.3$ and a cluster probability of $p < .05$, corrected for whole-brain multiple comparisons, are reported and shown in figures. For visualization purposes, statistical maps of all analyses were projected onto the study-specific average brain of the participants.

Functional connectivity in putative emotion regulation networks were examined using psycho-physiologic interaction (PPI) analyses (Friston, Buechel, Fink, et. al., 1997). The aim of these analyses was to examine fronto-limbic connectivity during affective labeling. The PPI analysis consists of a design matrix with three main regressors: the "psychological variable," representing the experimental task (here, either *affect-label* versus *gender-label* or *affect-label* versus *affect-match*); the "physiological variable," representing task-related brain response (i.e., BOLD percent signal change) in a priori regions of interest (ROI) or seed regions (here vlPFC); and a third variable representing the interaction between the first and the second variables. Movement parameters, incorrect trials and trial time remaining after a participant made a response were modeled out as nuisance variables, as in the original model.

ROI in subcortical regions were defined anatomically based on the Harvard-Oxford probabilistic subcortical structural atlas. Cortical ROI were defined based on areas of overlap between functional activation and anatomically-defined regions based on the Harvard-Oxford probabilistic cortical structural atlas. Bilateral regions were selected given that the task includes both faces and words and so as not to bias analyses toward a small set of lateralized regions across task conditions. The ROI were defined at the group level in standard space and were projected back to the native space of each individual subject. A variable representing the

interaction between each time series and the psychological variable (e.g., *affect-label* versus *affect-match*) was constructed for each subject. Voxel-wise PPI analyses were conducted for between and within group effects using the same multi-stage general linear model approach with FEAT as described above for fMRI analysis. Mean activation of results for each group is displayed in graphs for ease of visualization purposes only.

A primary objective of the current study was to test a model of overlap versus differentiation of aberrant processing relative to healthy controls between the two diagnostic groups. In terms of imaging data, this model may be tested in two ways. For one, and most simply, when diagnostic groups are contrasted directly against each other, there would be evidence for differentiation if between groups differences were observed. However, a lack of significant difference between diagnostic groups does not allow for inference of similarity across groups with any degree of certainty. We therefore also tested overlap versus differentiation by comparing difference maps of each group versus controls. A model of overlapping abnormality would predict a pattern of fMRI activation which demonstrates that differences relative to controls is similar across patient groups, such that a comparison of difference maps for each group versus controls would show overlap in voxels sensitive to the difference. If, on the other hand, both groups differ from controls but in different ways, and for different neurofunctional reasons, then those difference maps would be expected to show little similarity.

In the same way, similarly normative processing observed in activation maps for each group by condition could also prove informative. Conjunctive analysis of activation maps predicted by a model of overlap should demonstrate a pattern of fMRI activation in which the diagnostic groups are similar in terms of regions in which they demonstrate overlapping

activation relative to controls. In order to compare difference and activation maps, we used the Dice similarity measure (DSM) (Dice, 1945), a symmetric index of the resemblance of two binary images that has been employed in previous work to measure the number of activated voxels that are shared between two fMRI images (Salimi-Khorshidi et. al., 2009). The DSM coefficient ranges from 0 (indicating no overlap) to 1 (perfect overlap). The DSM coefficient was calculated for each condition of interest for both activation and functional connectivity maps with the following equation:

$$DSM=(2 \times |A \cap B|) / (|A| + |B|)$$

where A represents, for example, the z-statistic difference map from one patient group versus controls and B represents the z-statistic difference map from the other patient group versus controls. For comparison of activation maps, A represents the z-statistic map from one patient group plus controls and B represents the z-statistic activation map from the other patient group plus controls.

A secondary aim of the current study was to assess the relationship between symptom severity, behavioral task performance, and associated fMRI activation abnormalities observed in a priori regions of interest. Average COPE (contrast of parameter estimates) values were extracted from pre-defined ROIs and used in mixed models analyses of variance with repeated measures for the two patient groups only. We focused on task performance across the two emotion conditions of primary interest, and used the *FM* contrast to further isolate emotion processing (i.e., *AL-FM, AM-FM*). Fixed effects included clinical measures, accuracy, and reaction time; age and sex were entered into the models as covariates. The group variable was also included to assess whether effects differed by patient group (i.e., interaction effects). In the presence of such interactions, simple effect analyses were performed, and significant group

effects were evaluated with post-hoc t-tests. All analyses measured significance at the .05 level (two-tailed, unless otherwise noted). Analyses were conducted in SPSS; each ROI was modeled separately for these analyses.

VI. RESULTS

6.1. Behavioral Results

6.1.a. Accuracy: Repeated measures mixed effects model revealed a significant interaction between group and task condition ($F(8,140) = 4.69$, $p < .001$). Results are displayed in Figure 1. Tests of simple effects demonstrated significant group differences in accuracy on three of the five conditions (*affect-label*: $F(2,139)=6.47$, $p<.005$; *affect-match*: $F(2,138)=19.51$, $p<.001$; *gender-match*: $F(2,141)=3.57$, $p<.05$). In particular, both patient groups showed reduced performance on the affect conditions relative to healthy controls (SCZ vs controls: *affect-label*: $t(139)= -3.35$, $p<.005$; *affect-match*: $t(138)=-4.59$, $p<.001$; BD vs controls: *affect-label*: $t(139)= -2.49$, $p<.05$; *affect-match*: $t(138)=-3.11$, $p<.005$), in line with the hypothesis that both groups would demonstrate poor performance during tasks of facial affect recognition. The patient groups were indistinguishable on the *affect-label* condition, whereas SCZ patients showed reduced performance relative to BD patients on *affect-match* ($t(139)=-2.67$, $p<.01$). Further, SCZ patients were impaired on the *gender-match* condition relative to controls ($t(140)=-2.64$, $p<.01$), whereas BD patients were indistinguishable from controls; BD patients were not significantly different from SCZ patients on the *gender-match* condition.

6.1.b. Reaction Time: Repeated measures mixed effects model revealed a significant main effect of group ($F(2,138) = 3.50$, $p<.05$) as well as an interaction between group and task condition ($F(8,139) = 7.85$, $p<.001$). Tests of simple effects demonstrated significant group differences in

RT on all conditions (see Figure 2). In particular, SCZ patients were markedly slower across all task conditions relative to BD patients and healthy controls, except the form match condition, in which SCZ patients did not differ from BD patients. BD patients were significantly slower than controls on *affect-label*, *affect-match, and gender match.* They were indistinguishable from controls on *gender-label* and *form-match*.

In addition, there was a significant linear relationship between age and RT ($F(1,136)=18.43$, $p<.001$). Specifically, a 1-year increase in age was associated with an increase of 8.57ms in overall RT across tasks ($t(144)=2.97$, $p<0.005$). This relationship did not vary by group or task condition ($F(4,139)=2.22$, $p=.07$).

Multiple regression analysis was used to examine the relationship between task performance and scores on symptom measures within and across patient groups by condition. Across patient groups, only performance during *affect-match* was significantly correlated with symptoms, in terms of both accuracy and RT (accuracy: $F(6,70)=3.12$, $p<.01$; RT: $F(6,70)=3.08$, $p=.01$). Furthermore, *AM* accuracy and RT were only significantly predicted by total SANS score (accuracy: $F(1,76)=5.43$, $p<.05$; RT: $F(1,76)=7.44$, $p<.01$). In particular, a 1-point increase in SANS score was associated with a decrease in *AM* accuracy of .19% ($t(70)=-2.40$, $p<.05$) and an increase of 5.87ms in *AM* RT ($t(70)=2.78$, $p<.01$). Scores on SAPS, HAMD, and YMRS symptom scales were not significant predictors of either accuracy or RT. The overall model explained 23.3% of the variance in *AM* accuracy ($R^2=0.23$, $F(6,70)=3.54$, $p<.01$) and 20.3% of the variance in *AM* RT ($R^2=0.20$, $F(6,70)=2.98$, $P<.05$). The effect for *AM* accuracy did not vary by group whereas the effect for *AM* RT was greater in the BD group than the SZ group ($F(1,72)=4.82$, $p<.05$). Relationships between symptom severity and fMRI activations were also explored (see below).

6.2. Neuroimaging Results

6.2.a. Whole-brain Voxel-wise Analysis: In order to assess differences in fMRI activation by diagnostic groups, individual task conditions of interest were examined. Each of the four primary conditions of interest was modeled against the *form-match* condition as a baseline control condition (thus removing visual and motor effects unrelated to facial and emotion processing; e.g., *affect-match* versus *form-match* (*AM-FM*)). For a manipulation check, Table 2 provides a complete listing of coordinates by *FM* contrast for the control group.

The Dice index was calculated for activation maps of each *FM* contrast comparing degree of overlap in regions similarly activated in each diagnostic group relative to controls. The greatest overlap in regions of activation was found for the *AM-FM* contrast (DSM = 0.82), followed by *GM-FM* (DSM = 0.77), *AL-FM* (DSM = 0.68), and *GL-FM* (DSM = 0.61).

The behavioral results summarized above indicated that patients were impaired on accuracy relative to controls most severely during *affect-match.* In parallel with those findings, significant between-groups differences in BOLD signal were observed for the *AM-FM* contrast. In particular, control individuals demonstrated greater activation than both patient groups in bilateral pre- and post-central gyrus and posterior cingulate gyrus (BA23, ventral and BA31, dorsal) when the two groups were entered into combined contrast versus controls (Figure 3, green). The effect was largely carried by BD patients, who showed greatest effect of reduced activity in posterior cingulate and left post-central gyrus versus controls (Figure 3, red). In contrast, SCZ patients showed reduced activation relative to control participants in right amygdala and right hippocampus (Figure 3, blue). As such, the Dice index for the difference maps of each group relative to controls revealed no overlap (DSM = 0.0). Although patients were

also impaired on *affect-label* and *gender-match* conditions, no group differences in fMRI activation were observed for the *AL-FM* or *GM-FM* contrasts.

In line with previous studies (e.g., Mahon, et. al., 2012; Meda, et. al., 2012) we performed post hoc analyses in which we separated out BD individuals with psychotic symptoms (i.e., those who endorsed presence of positive symptoms), comparing ROI percent signal change during each task condition (i.e., *FM* contrasts) between the BD subgroups, SCZ patients, and controls. Of the 38 patients in the original BD group, 16 were separated out, having been rated as positive for psychotic symptoms on the SAPS scale. We expected greater overlap in patterns of activation differences between SCZ patients and this subset of BD patients relative to controls; however, only activity in the right amygdala ROI corresponded to significant group differences ($F(3,137)=3.02$, $p<.05$), and the psychotic BD group actually showed greater disparity (i.e., elevated right amygdala activation) relative to SCZ patients ($t(137)=2.72$, $p<.01$) and controls ($t(137)=2.89$, $p<.01$) than non-psychotic BD patients, who were not significantly different from SCZ patients or controls. This difference did not vary by *FM* condition contrast. We also tested this effect in BD patients who endorsed negative symptoms, with nearly identical results.

Previous studies have observed reduced amygdala and greater vlPFC activation during *affect-label* relative to *gender-label* in healthy subjects. To isolate activation specific to affective labeling, the *affect-label* condition was modeled against the *gender-label* condition (i.e., *AL-GL)*. In line with previous findings, control participants demonstrated greater vlPFC (inferior frontal gyrus, BA 47, 44, 45) activity during *AL* versus *GL* in left hemisphere (Figure 4a, yellow). SCZ patients showed a different pattern, with greater activation for *AL-GL* in posterior temporal regions including left angular gyrus, left lateral superior cortex, superior division (BA19), left middle temporal gyrus, posterior division and temporo-occipital part and right superior and

middle temporal gyrus, posterior division (Figure 4a, dark blue). In direct comparison to controls, patients with SCZ demonstrated greater activation in right angular gyrus (BA22), right middle temporal gyrus, right superior temporal gyrus (BA 21), bilateral precuneous cortex and (BA30), left fusiform gyrus (BA 37), intracalcarine cortex, left thalamus, and left hippocampus (figure 4b, dark blue). No significant differences were observed in BD individuals relative to controls. In direct comparison with BD patients, activation for the SCZ group was greater in right middle temporal gyrus and right superior temporal gyrus (BA 21/22) (see figure 4b, light blue).

6.2.b. PPI Analysis: A primary question of interest to the current study was whether direct assessment of functional connectivity during affective labeling would reveal an inverse functional relationship between fronto-limbic regions thought to be associated with emotion regulation processes, and whether this connectivity would be disrupted in patient groups. Therefore, we examined PPI for the primary *AL-AM* and *AL-GL* contrasts of interest. We used left and right vlPFC as the seed regions for this portion of the analysis.

AL-AM, Left vlPFC: Patients with SCZ showed significant positive functional connectivity for left vlPFC with left insula, left putamen, and left temporal pole during *Affect-Label* versus *Affect-Match* (Fig 5a). No significant positive functional connectivity with left vlPFC was observed in the control or BD groups. In direct comparison to control individuals, SCZ patients demonstrated positive functional connectivity whereas controls demonstrated negative (i.e., inverse) connectivity for left vlPFC with areas of left superior parietal lobule, left supramarginal gyrus, posterior division (BA40), left lateral occipital cortex, and precuneus (BA7) for this contrast (see Figure 5b). No significant group differences were observed between BD patients and controls or BD and SCZ patients.

AL-AM, Right vlPFC: In direct comparison to control individuals, BD patients demonstrated positive functional connectivity whereas controls demonstrated inverse functional connectivity for right vlPFC with anterior lingual gyrus/ventral precuneus for the *AL-AM* contrast (Figure 7). In contrast, direct comparison of controls and SCZ patients revealed positive functional connectivity in right vlPFC with left supramarginal gyrus, posterior division (BA40), left superior parietal lobule, left lateral occipital cortex, superior division and precuneus (BA7), in both groups, but connectivity was significantly greater in SCZ patients (Fig 6). The Dice index between the difference maps of each group relative to controls revealed no overlap (DSM = 0.0). Furthermore, BD patients demonstrated differences in functional connectivity versus SCZ patients for right vlPFC in two regions. In precuneus (BA19/31) they had less positive functional connectivity than SCZ patients (Figure 8a). In addition, both groups demonstrated inverse connectivity with left middle frontal gyrus (BA8/9) and left precentral gyrus (BA6) but this effect was greater in SCZ patients (Figure 8b).

AL-GL : During *Affect-Label* versus *Gender-Label,* all patients showed inverse functional connectivity in both left (Fig 9, pink) and right (Fig 9, dark red) vlPFC with left supramarginal gyrus (BA40) and left angular gyrus (BA 39). Across groups, there was additional inverse functional connectivity for left vlPFC with medial frontal gyrus/paracingulate gyrus (BA9; dlPFC), whereas for right vlPFC there was further inverse connectivity with superior temporal gyrus (BA22), posterior portion, across groups. No between groups differences were observed for this contrast.

6.3. Symptoms, Accuracy, and ROI Data

We examined associations between ROI percent signal change, task performance, and symptom severity scores across emotion conditions versus the *form-match* control (i.e., *AM-FM* and *AL-FM*) in patient groups only.

Amygdala: Repeated measures mixed effects model revealed a significant relationship between total SAPS score and activity in left amygdala ($F(1,66)=4.45$, $p<.05$). The relationship did not vary by patient group or by condition. Specifically, a 1-point increase in SAPS score was associated with .05 unit increase in left amygdala activation ($t(70)=1.78$, $p=.08$) across groups. These results are displayed in Figure 10a. In contrast, a significant interaction of group by total SANS score was observed for right amygdala ($F(1,63) = 3.94$, $p=.05$) indicating that the relationship between negative symptomatology and right amygdala activity varied by group (see Figure 10b). Specifically, a 1-point increase in SANS score was associated with .03 unit increase in right amygdala activation across groups ($t(63)=1.94$, $p=.06$). This effect was reduced in SCZ patients relative to BD patients ($t(63)=-1.99$, $p=.05$). No correlation between left or right amygdala and task performance (accuracy or RT) was observed.

vlPFC: No association of left or right vlPFC with symptoms scores or task performance across the affect recognition conditions was observed.

dlPFC: Repeated measures mixed effects model revealed a significant group by total YMRS score cross-over interaction effect on activity in both left ($F(1,65) = 6.50$, $p<.05$) and right ($F(1,65) = 4.10$, $p<.05$) dlPFC such that an increase in mania symptoms was associated with an increase in dlPFC activation for BD patients, but a decrease in dlPFC activation for SCZ patients (See Figures 11a and 11b). Specifically, for SCZ patients a 1-point increase in YMRS score was associated with a .06 unit decrease in left dlPFC activation relative to the BD group

($t(65)=-2.55$, $p<.05$) and a .06 unit decrease in right dlPFC activation relative to the BD group ($t(65)=-2.02$, $p<.05$).

VII. DISCUSSION

Aim 1, Overlap vs Differentiation

The major aim of the current study was to examine both behavioral and neural correlates of deficits in facial affect recognition and disruptions in regional neural activity required for successful incidental emotion regulation in patients with SCZ and BD patients in order to ascertain whether there is greater evidence of phenotypic overlap or differentiation between the patient groups relative to healthy controls in the emotion processing domain. We predicted a mixed pattern of primarily overlap between the two disorders, with similar behavioral deficits and corresponding neural activity differences relative to controls expected on affect recognition tasks. We predicted some evidence of differentiation owing to deficits in basic face perception unique to SCZ patients, which would be observed during the matching relative to labeling tasks. On the contrary, our findings indicated that, while behavioral data was suggestive of an overall pattern of mostly similarity consistent with our predictions, the pattern revealed by corresponding neurofunctional activity was one of mostly differentiation between the two patient groups. Specifically, differing regions of hypoactivity during affect matching and hyperactivity during affect labeling were observed, as well as distinct patterns of aberrant functional connectivity. Specifics of these findings are discussed below.

Behavioral data: As predicted, SCZ patients showed greater impairment than BD patients on tasks requiring perceptual feature comparisons across multiple images. As such, performance in the SCZ group was impaired during the *gender-match* condition relative to controls, whereas

performance among BD patients was not. This impairment was in line with expectations given the difficulty SCZ patients have with basic perceptual processing of faces demonstrated in prior literature (e.g., Doop & Park, 2009; Rocca, et. al., 2009). Interestingly, participants with BD were not significantly different from those with SCZ on this condition, indicating that their performance fell between that patient group and controls. In contrast, SCZ patients showed greater deficits than BD patients on *affect-match,* a task condition which compounds required emotion processing with perceptual processing, likely owing to the increase in cognitive load.

As predicted, individuals from both patient groups demonstrated reduced performance relative to healthy control individuals during the two explicit tasks of affect recognition, namely affective labeling and affective matching. The patient groups were indistinguishable in terms of accuracy on the *affect-label* condition, whereas SCZ patients showed further impairment during *affect-match*. As noted above, given that the SCZ group also showed impairment during *gender-match,* unlike BD patients, the additional differences are likely attributable to additional deficits in perceptual processing and corresponding increased cognitive load, rather than any additional deficits in affect recognition per se.

Consistent with our predictions, task performance across conditions was not correlated with residual manic or depressive symptoms in individuals with BD disorder (all in a euthymic state in the current study) or presence of these symptoms in individuals with SCZ (though no predictions were made regarding manic or depressive symptoms in SCZ participants). Contrary to expectation, performance was not correlated with positive symptoms in SCZ participants or BD participants (predictions were also not made about this effect in BD individuals). However, as predicted, negative symptoms were negatively correlated with task performance (higher scores were associated with lower accuracy, increased reaction time), and this was again the case for

both patient groups. Interestingly, this effect was greater in the BD group, perhaps reflective of a greater degree of impairment in more severe cases of illness.

Thus, based on behavioral data alone, there is evidence to suggest a significant amount of homology between patient groups in the domain of emotion processing, with poor affect recognition in terms of both labeling and matching across groups, relative to controls.

Imaging data: Corresponding neuroimaging data showed minimal evidence for similarity in neurofunctional activity underlying demonstrated behavioral deficits. There was some overlap in regions hypoactive relative to controls for the *AM>FM* contrast. Both patient groups demonstrated less activation in bilateral pre- and post-central gyrus and posterior cingulate gyrus than the control group. Posterior cingulate, in particular, has been shown to mediate interactions of emotional and memory-related processes (Maddock, Garrett, & Buonocore, 2003). More recent literature classifies posterior cingulate as a core feature of social cognitive networks, including those involved with representations of the self and others (for a review, see Jimenez, Gee, Cannon, & Lieberman, 2012) or default mode network (Buckner, Andrews-Hanna, & Schacter, 2008; Leech, Kamourieh, Beckmann, & Sharp, 2011), discussed further below. However, when compared to controls individually, this effect was primarily found in the BD group, whereas SCZ patients showed significant hypoactivation in subcortical limbic regions, including amygdala.

Hypoactivation of amygdala during affect perception is consistent with previous findings for SCZ patients (e.g., Williams, et. al., 2007; Taylor, et. al., 2005; Kohler & Brennan, 2004; Gur et. al., 2002) and may reflect difficulty in the automatic evaluation of salient (emotional) or ambiguous stimuli (e.g., Whalen et. al., 2001; Kesler-West et. al., 2001), or failure in subsequent coordination by amygdala of complex neurophysiological response to such stimuli (e.g.,

Adolphs, 2003; Vuilleumier & Pourtois, 2006; LeDoux, 2000). Contrary to our hypothesis, BD patients did not show a reduction in amygdala activity in either affect recognition conditions. Therefore, these findings would seem to suggest that both patient groups demonstrate hypoactivation in areas critical for effective affect recognition, which may underlie poor performance in both groups, but these areas are not entirely the same across the two groups.

During processing specific to affective labeling (i.e., *AL>GL*), only SCZ patients showed differences in patterns of activation relative to controls, and they also showed differences relative to BD patients in direct comparison with that group. In particular, in comparison to controls, SCZ patients demonstrated a failure to modulate subcortical regions; although not the amygdala specifically, as we predicted, the SCZ group showed hyperactivation of other lower-level regions involved in face processing, such as fusiform gyrus, intracalcarine cortex in inferior occipital cortex, and posterior superior and middle temporal gyrus (Kanwisher, McDermott, & Chun, 1997; Rossion, et. al., 2003; Engell & Haxby, 2007; Haxby et. al., 2000). A subset of these regions (i.e., right middle temporal gyrus and right superior temporal gyrus) was also more active in SCZ patients than BD patients when compared directly. On the other hand, BD patients were not significantly different from controls for the *AL>GL* contrast.

Further investigation of inter-cortical and cortico-subcortical connectivity modulation by task was completed with PPI analysis. Several distinct brain networks demonstrating temporal coherence in the fMRI timecourse have been identified during both periods of extended rest (e.g., Raichle, 2011; Power, Cohen, Nelson, Wig, & Barnes, et. al., 2011) and during a given task (Calhoun, Kiehl, & Pearlson, 2008). These include the default mode, fronto-parietal (FP), and salience (SAL) networks, among others. These networks have been shown to be reliable and robust; experimental manipulation via a directed task offers a means by which to examine how

networks may be spatially and temporally modulated (Calhoun, et. al., 2008), as well as a window into pathophysiology of psychiatric illness by examination of within and across network functional dysconnectivity (Mamah, Barch, & Repovs, 2013).

The default mode network (DMN) is thought to support introspective, task-independent thought, future planning, and attention to internal, emotional states. DMN generally includes midline regions within posterior cingulate cortex, precuneus, and mPFC; baseline activity in these regions decreases with engagement in a variety of goal-directed, cognitive activation paradigms (Raichle, Macleod, Snyder, Powers, Gusnard, & Shulman, 2001). SCZ patients have demonstrated altered connectivity within the DMN network (Garrity, Pearlson, McKiernan, Lloyd, Kiehl, & Calhoun, 2007) and failure to deactivate DMN (Pomarol-Clotet, Salvador, Sarro, Gomar, & Vila, et. al., 2008) as required for adequate task engagement and efficient performance (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003). The SAL network, which includes dorsal anterior cingulate, anterior insula, and anterior PFC, is thought to activate in response to salient sensory input, such as pain, hunger, or pleasurable touch (Seeley, Menon, Schatzberg, Keller, & Glover, et. al., 2007). Some prior research suggests that aberrant salience is involved in generation of delusions and hallucinations in SCZ patients (White, Joseph, Francis, & Liddle, 2010). Finally, the FP or executive control network allows for conscious directing of attention toward pertinent information, set maintenance, and response flexibility. It involves regions of dlPFC, dmPFC/pre-SMA, and vlPFC (Seeley, et. al., 2007).

As such, our task of affective labeling would seem to require disengagement of DMN and engagement of FP network operations, as, broadly, this task requires cognitive control over sensorimotor representations, maintenance of relevant data, and response selection and suppression. More specifically, involvement of language may recruit areas of PFC with a

corresponding decrease in limbic structures such as amygdala. SCZ patients showed aberrant functional connectivity patterns during *AL>AM.* Specifically, SCZ patients demonstrated positive functional connectivity whereas controls demonstrated null or negative (i.e., inverse) connectivity for left vlPFC with areas of left superior parietal lobule, left supramarginal gyrus, left lateral occipital cortex, and precuneus; both controls and SCZ patients demonstrated positive functional connectivity in right vlPFC with left supramarginal gyrus, left superior parietal lobule, left lateral occipital cortex, and precuneus, but connectivity was significantly greater in SCZ patients. These findings in SCZ patients may reflect not only a lack of dis-engagement of DMN during the task, but also failure of frontal regions to modulate posterior and subcortical structures and/or compensatory strategies to overcome faulty FP network functional connectivity via recruitment of additional parietal association cortices.

In contrast, BD patients demonstrated inverse functional connectivity whereas controls demonstrated positive functional connectivity for right vlPFC with anterior lingual gyrus/ventral precuneus for the *AL>AM* contrast, evidence of a more direct functional dysconnectivity in BD patients for this network. BD patients demonstrated differences in functional connectivity versus SCZ patients for right vlPFC in two regions, one frontal and one posterior. BD patients demonstrated differences in functional connectivity versus SCZ patients for right vlPFC in two regions, one frontal and one more posterior. In frontal regions, specifically SCZ patients showed connectivity between right vlPFC and left middle frontal gyrus and left precentral gyrus, whereas BD patients did not. Posteriorly, both groups demonstrated inverse connectivity between vlPFC and precuneus but this effect was greater in SCZ patients. Taken together, these finding indicate cortico-cortical connectivity in frontal regions for SCZ patients but not BD patients, along with greater negative connectivity between fronto-parietal regions in SCZ versus BD patients.

Evidence for overlap versus differentiation of aberrant processing in diagnostic groups relative to healthy controls was most directly tested when the groups were contrasted against each other. Based on these contrasts, we found some evidence for differentiation between SCZ and BD. In particular, during *AL>GL*, right middle temporal gyrus and right superior temporal gyrus, brain regions involved in face processing, were more active in SCZ patients than BD patients when compared directly, perhaps indicative of failure of fronto-limbic circuitry to modulate lower-level regions during affective labeling, present in the SCZ but not the BD group. Furthermore, PPI analysis of the AL>AM contrast revealed aberrant cortico-cortical connectivity in frontal regions for SCZ patients but not BD patients, along with greater negative connectivity between fronto-parietal regions in SCZ versus BD patients. No other task contrasts elicited significant differences when the two patient groups were compared directly. However, as noted previously, a lack of significantly different findings does not necessarily equate to the two groups being the same and it is difficult to ascertain from the two specific findings to what degree the two groups differ overall.

Accordingly, the model of overlap versus differentiation was also tested by comparing difference maps of each group versus controls as well as conjunctive analysis of activation maps for each group by condition. The results of these analyses provided further evidence in support of a model of differentiation in the neurophysiology underlying emotion processing deficits, indicating that, when both groups differed from controls, they did so for different neurophysiological reasons. As such, the difference maps of each group relative to controls showed no similarity between them. Comparison of degree of normative processing was less discriminating between the two patient groups, though conjunctive analysis still indicated only moderately similar patterns of overlap in fMRI activation in each group relative to controls.

Aim 2, Emotion processing deficits, symptomatology, and neurophysiology

A secondary aim of the current study was to assess the relationship between emotion processing deficits, clinical features of illness, and neural activity within patient groups. We thus examined whether fMRI activation in discrete ROI was predicted by task performance and symptoms. Consistent with predictions regarding BD patients, but contrary to our predictions regarding SCZ patients, fMRI activation was not directly related to accuracy on any task condition for either patient group. However, we found that fMRI activations were correlated with symptom severity measures.

In particular, as the level of positive symptoms (i.e., SAPS score) increased, left amygdala activation increased, across task conditions for both SCZ and BD groups. Activation in right amygdala was shown to increase with an increase in negative symptoms (i.e., SANS score) across tasks and for both patient groups, though this effect was greater for BD individuals. This effect is noteworthy, given that SCZ patients demonstrated hypoactivation of amygdala during emotion matching, specifically, a task with which they had considerable difficulty. It could be that greater symptom severity was associated with failure to modulate amygdala activity during labeling tasks for both patient groups. However, interpretations are difficult to argue with any certainty, given that this effect did not very by task condition. The interactive effect for SANS scores and left amygdala also suggests that the result may be carried by the effect in the BD group.

In contrast to psychotic symptoms, symptoms of mania were not related to amygdala activation; however, they were associated with activation in dlPFC, an area of dense cortical circuitry known to be critical for selective attention and other aspects of executive functioning via top-down cognitive control processes (e.g., MacDonald, Cohen, Stenger, & Carter, 2000).

This effect varied by group such that an increase in mania symptoms was associated with an increase in dlPFC activation for BD patients, but a decrease in dlPFC activation for SCZ patients. These findings suggest a differential effect of manic symptoms by patient group whereby cognitive efficiency and control processes are enhanced by residual mania symptoms in euthymic BD individuals but degraded by such symptoms in individuals with SCZ. This finding in BD patients is consistent with prior literature suggestive of enhanced creativity and other aspects of cognitive functioning in BD patients (Soeiro-de-Souza, Dias, Bio, Post, & Moreno, 2011; Andreason, 1987) and their un-affected co-twins (Higier, Jimenez, Hultman, Borg, & Roman, et. al., submitted).

To further assess the impact of severity of illness in BD (i.e., psychotic features) in terms of overlap with SCZ, we separated out BD individuals who endorsed presence of positive symptoms and performed post hoc analysis of ROI percent signal change comparing those individuals to the SCZ and control groups. Recent studies directly comparing neural systems associated with emotion processing deficits in SCZ and BD have compared patients with SCZ to patients with psychotic BD (e.g., Mahon, et. a., 2012; Meda, et. al., 2012), no doubt based on the idea that such patients may constitute a BD subgroup that is more similar to SCZ. Such analysis would seem to better tap into a putative psychosis dimension that, if it exists, may cross diagnostic boundaries. However, we found that separating out BD patients who endorsed positive symptoms actually served to further discriminate that group from both healthy controls and SCZ patients, although only in terms of percent signal change in a right hemisphere amygdala ROI. Interpretations based on the current analysis are thus limited.

In summary, we found evidence that overt behavioral impairment in affect recognition, rather than distinguish between SCZ and BD, constitutes another area of phenotypic overlap

between the two disease states. These extend previous research findings of phenomenological overlap between the two disorders (e.g., Lin & Mitchell, 2008). However, we found little evidence for corresponding similarity in neurophysiology underlying those deficits. Rather, the current findings tended to lend more support for differentiation, in line with previous findings comparing SCZ and BD patients on neuroimaging measures (e.g., Morris, et. al., 2012; Lui, et. al., 2013; Chai, et. al., 2011).

Taken together, these conflicting findings would appear to render the matter of overlap versus differentiation unresolved. On the one hand, there is a case to be made for the strong reliability of overt behavior and the ability of experimental paradigms to parse out subtle aspects of performance deficits. However, given evident redundancy in neural systems processing, one can imagine it likely that similar behavioral endpoints are often achieved with very different physiological correlates. In fact, our utilization of neuroimaging methods is based largely on the assumption that there is significant, and perhaps greater, insight into overt behavior achieved by understanding the neurofunctional processing that subserves it. In this way, the pattern of differentiation suggested by these physiological data might be said to carry more weight.

In addition, another and perhaps most telling piece of evidence in support of a differentiation model is the fact that the psychotic BD patients in our sample were even more different from the SCZ patients than those with non-psychotic BD. That a similar profile of symptomatology would actually enhance differences in the neuronal profiles between the two groups gives strong indication that underlying physiology and thus core processing systems within this domain would appear to be markedly different in BD as compared to SCZ.

Several important limitations to the current study bear mention. First, our version of the affective labeling paradigm was modeled after Lieberman, et. al. (2007). Importantly, however,

that version included an *observe* condition, during which participants were instructed to simply observe a single, emotionally expressive face without making a response. This condition was included for several reasons aimed at providing better comparison control conditions than the original task design; it also provided a condition which elicited robust amygdala activation. Including the *observe* condition thus allows for confirmation of amygdala localization, critical to a study of amygdala-PFC functional coupling, especially one examining patients known to demonstrate structural brain abnormalities (e.g., Andreasen et. al., 1994; Cannon, et. al., 1998; Beyer & Krishnan, 2002; Altshuler et. al., 1998; Mahon, et. al., 2012). It could thus be argued that our lack of findings in relation to differences in amygdala activation across tasks and by group were driven by a lack of anatomical spatial specificity in both whole-brain and ROI analyses rather than an actual lack of activation difference.

Furthermore, we explored functional connectivity between frontal and limbic regions with PPI, a valid approach but one not without limitations. Explicit testing of rsFC in a more exploratory manner utilizing a data-driven approach such as independent component analysis (ICA; McKeown & Sejnowski, 1998) might have further validated the current findings and offered additional insights into the nature of neural network disruptions in the two diagnostic groups.

In addition, we targeted for analysis a subgroup of psychotic BD patients and found further evidence of differentiation from SCZ patients in neurophysiology underlying emotion processing deficits. As these analyses were post hoc, time constraints limited the analysis to ROI percent signal change differences, and we did not perform whole-brain voxel-wise analysis of fMRI activation with this group separated out, nor did we examine functional connectivity differences within this group. Based on the current findings, these patients evidently do not fall

closer to SCZ patients along a putative underlying psychosis spectrum. It is possible that the manifestation of positive symptoms in individuals with BD disorder is based on some qualitatively different underlying process. On the other hand, it could be that the limited analysis of this subset of patients provides only a partial picture of the nature of those underlying processes, not allowing for compelling interpretations at the present time. In any case, further investigation is warranted and may add greatly to our understanding of the interactions between psychosis, disorder, and emotion processing deficits in patients.

Notably, the aims of the current study as a whole were necessarily limited to investigation of emotion processing as an area of phenotypic characterization of SCZ and BD. A model in which emotion processing could be explored as a marker of genetic liability or as an endophenotype for disorder would be a powerful tool in investigating whether dimensional constructs underlie these two disorders, benefitting from substantial prior evidence of genetic overlap between the two (e.g., Craddock, et. al., 2006; Ivleva, et. al., 2008). Recently study, Meda, et. al. (2012) did just that, including first-degree relatives of probands in their study of rsFC networks in SCZ and BD. In line with other studies reviewed previously, they found abnormal inter-network connectivity both unique to each patient group and shared between them. Further, a candidate endophenotype for BD but not SCZ (i.e., the pattern was not observed in SCZ relatives) was identified, such that BD relatives demonstrated reduced connectivity between anterior DMN regions, frontal, and higher-order visual regions in a manner similar to BD probands (and SCZ probands). More studies of unmedicated and unaffected relatives of probands such as this are needed to detect psychosis endophenotypes related to specific, measureable genetic risk factors and etiological pathways. In line with this, next steps in the current study are

to include analysis of fMRI data of unaffected cotwins of probands; affect recognition will thus be examined as a potential intermediate phenotype for BD and SCZ.

Organizing overt symptoms as continua of deficits may explicate specific phenotypic variation across an even broader spectrum of disorders. That is, if other abilities of the social domain (including affect recognition, but also social cognition, interpersonal skills, etc.) occur on a spectrum, then other disorders in which social functioning is disrupted (e.g., autism) would likely share genetic liability from genes associated with that domain. Likewise, if general or specific cognitive abilities fall along a spectrum, then other disorders comprising similar cognitive deficits (e.g., ADHD) may all share genetic liability from genes associated with the cognitive domain. This approach makes sense in the context of examining both mental illness and basic psychological processes from a dimensional perspective and warrants further investigation.

Despite the limitations, the current findings also have important clinical implications. In particular, the current study adds new and novel evidence to the ongoing debate regarding the utility of categorical classification of disease. In particular, it is clear that the current classification system does not fully capture the nuanced similarities and differences across diagnostic groups; yet, the nosology does appear to reflect underlying disparateness in neurophysiology, which is perhaps reflective of important differences in pathophysiology. Still, it is worthwhile to identify the nature of the similarities while recognizing the differences toward, for example, developing treatment targets.

To be sure, the current study has important implications for potential targets for intervention, for both BD and SCZ. For one, our findings suggest that underlying faulty patterns of fMRI activation are more related to symptom severity than overt behavioral impairment. We

know that a more holistic, biopsychosocial approach to intervention with an emphasis on social functioning as an outcome measure for both SCZ and BD patients has increasingly gained support (e.g., Lenior, Dingemans, Linszen, De Haan, & Schene, 2001; Gearing, 2008; Malkoff-Schwartz, 1998; Lam et. al., 2007; Beynon et. al., 2008; Miklowitz et. al., 2003). The current findings suggest that retaining symptom reduction goals, as well as incorporating neuronal measures, such as biofeedback, into psychosocial treatment modalities may further enhance effectiveness of these interventions.

VIII. APPENDIX

Table 1. Sociodemographic Characteristics by Group

Characteristic	Controls (n=64)		SCZ Patients (n=41)		BD Patients (n=38)		**Statistic**	**df**	***p* Value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**			
Age	48.6	9.8	49.4	10.6	49.6	10.2	$F = 0.14$	2,140	0.87
Years Education	13.2	3.0	13.4	3.1	12.7	3.0	$F = 0.46$	2,130	0.64
HAMD	2.33	3.7	8.23	5.1	5.24	7.5	$F = 15.1$	2,138	< 0.001
SANS	2.39	5.2	36.28	24.0	7.34	8.4	$F = 77.6$	2,138	< 0.001
SAPS	0.52	1.9	21.6	21.3	3.29	7.0	$F = 41.2$	2,138	< 0.001
YMRS	0.86	2.3	2.21	3.2	2.55	3.9	$F = 4.52$	2,138	< 0.05
	No.	**%**	**No.**	**%**	**No.**	**%**			
Female	34	53.1	17	41.5	24	63.2	$x^2 = 3.7$	2	0.15
Left-handedness	6	9.4	6	14.6	3	7.9	$x^2 = 1.1$	2	0.57
Medication Status							$x^2 = 69.4$	6	< .01
Anti-Psychotic	0	0.0	22	53.7	9	23.7			
Mood Stabilizer	0	0.0	1	2.4	10	26.3			
Anti-depressant	5	7.8	0	0.0	6	15.8			
Other or None	41	64.1	13	36.4	11	42.2			

Table 2. Peaks of Significant Clusters of Activation, Controls Only

Region	*X*	*Y*	*Z*	Max *Z*	Cluster size
Affect-Label > Form Match					
L Occipital Pole	-30	-94	-8	9.91	6961
B Lateral Occipital Cortex, inferior division					
B Occipital Fusiform Gyrus					
Lingual Gyrus					
L Inferior Frontal Gyrus, pars triangularis	-48	24	16	6.75	3710
L Inferior Frontal Gyrus, pars opercularis					
L Middle Temporal Gyrus, temporo-occipital part	-58	-54	6	5.26	1129
L Angular Gyrus					
R Middle Temporal Gyrus, posterior division	52	-30	-4	4.52	940
R Superior Temporal Gyrus, posterior division					
R Inferior Frontal Gyrus, pars triangularis	52	30	-2	4.92	780
Affect-Match > Form Match					
L Occipital Pole	-26	-94	-8	9.6	6486
B Lateral Occipital Cortex, inferior division					
B Occipital Fusiform Gyrus					
L Inferior Frontal Gyrus, pars opercularis	-52	12	14	5.06	1856
R Amygdala	18	-8	-16	4.6	1446
R Hippocampus					
Precuneous Cortex	2	-54	24	5.3	1149
Cingulate Gyrus, posterior division					
L Amygdala	-28	-10	-16	3.81	866
L Hippocampus					
Gender-Label > Form Match					
L Occipital Pole	-25	-94	-8	9.13	14210
B Lateral Occipital Cortex, inferior division					
B Occipital Fusiform Gyrus					
Lingual Gyrus					
L Inferior Frontal Gyrus, pars triangularis	-50	26	-4	5.13	2339
L Frontal Operculum Cortex					
Precuneous Cortex	2	-64	26	5.67	2112
Cingulate Gyrus, posterior division					
R Inferior Frontal Gyrus, pars triangularis	52	30	2	4.12	1124
Middle Frontal Gyrus					
Gender-Match > Form Match					
R Occipital Pole	16	-94	-4	9.64	10372
B Lateral Occipital Cortex, inferior division					
B Occipital Fusiform Gyrus					
Lingual Gyrus					
Precuneous Cortex	4	-66	28	5.58	1423
R Amygdala	18	-6	-20	5.45	1052
R Hippocampus					
L Inferior Frontal Gyrus, pars opercularis	-40	18	22	4.86	848
Temporal Pole	38	22	-24	4.44	606

X, Y, and Z MNI coordinates in millimeters indicate the location of peak voxel activation. Additional regions within the same cluster are listed following the strongest local maximum for that cluster. R, Right; L, Left; B, Bilateral

Figure 1. Mean Accuracy for Group by Condition

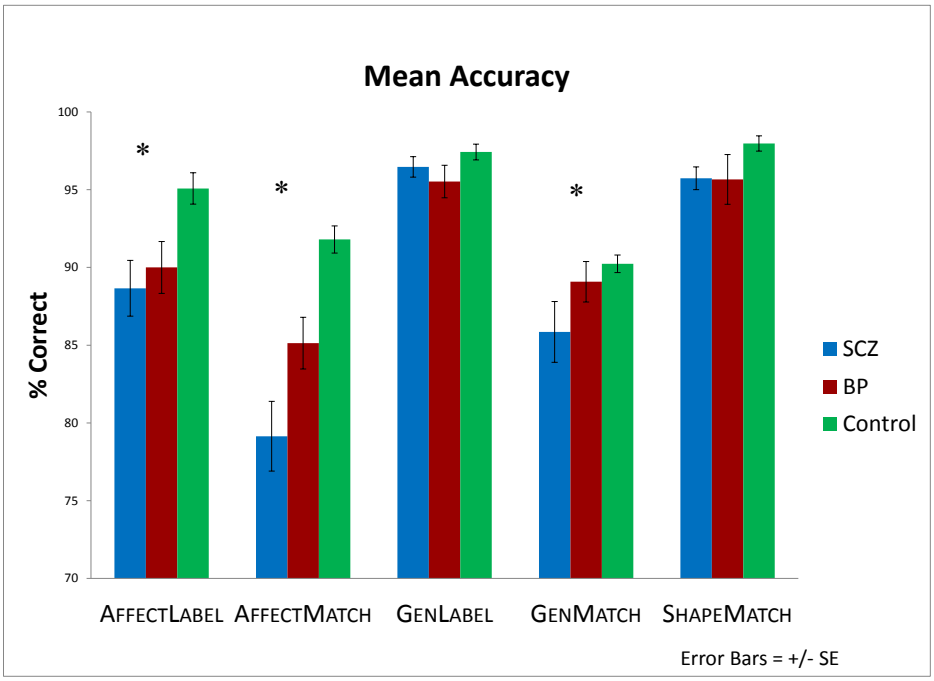


Figure 2. Mean Reaction Time for Group by Condition

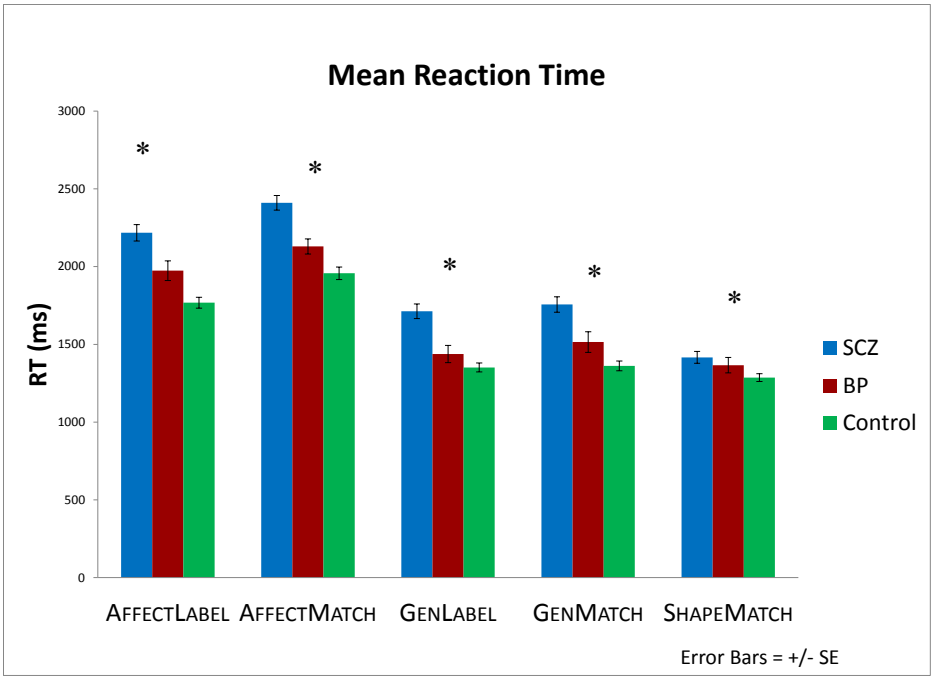
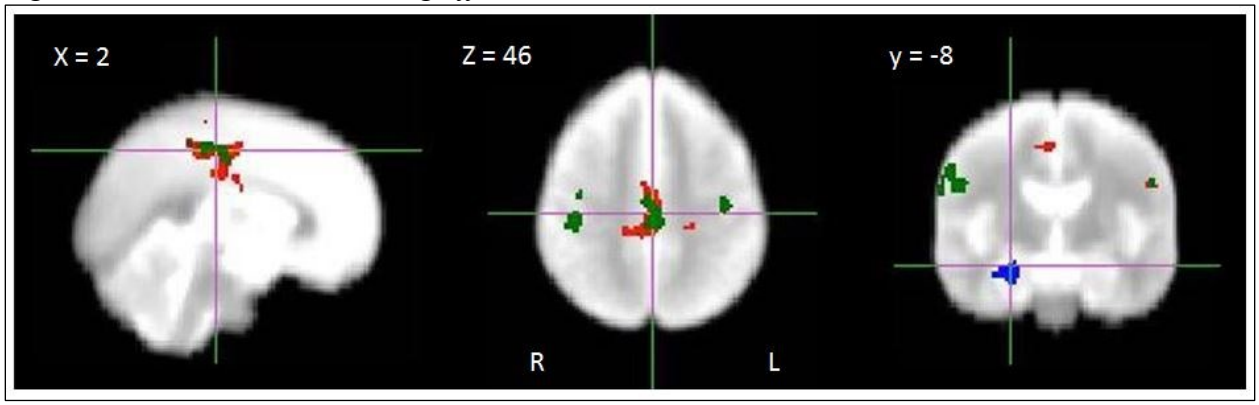
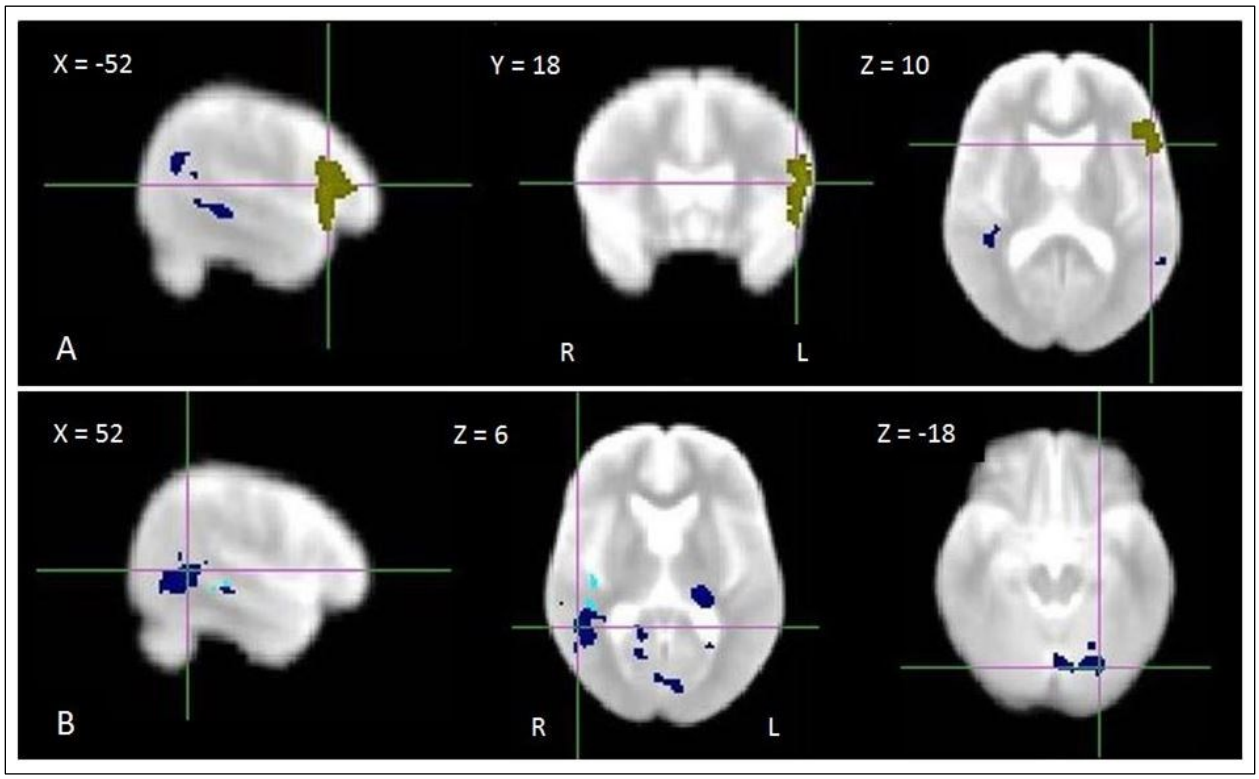


Figure 3. fMRI activations during *Affect-Match>Form-Match* contrast.



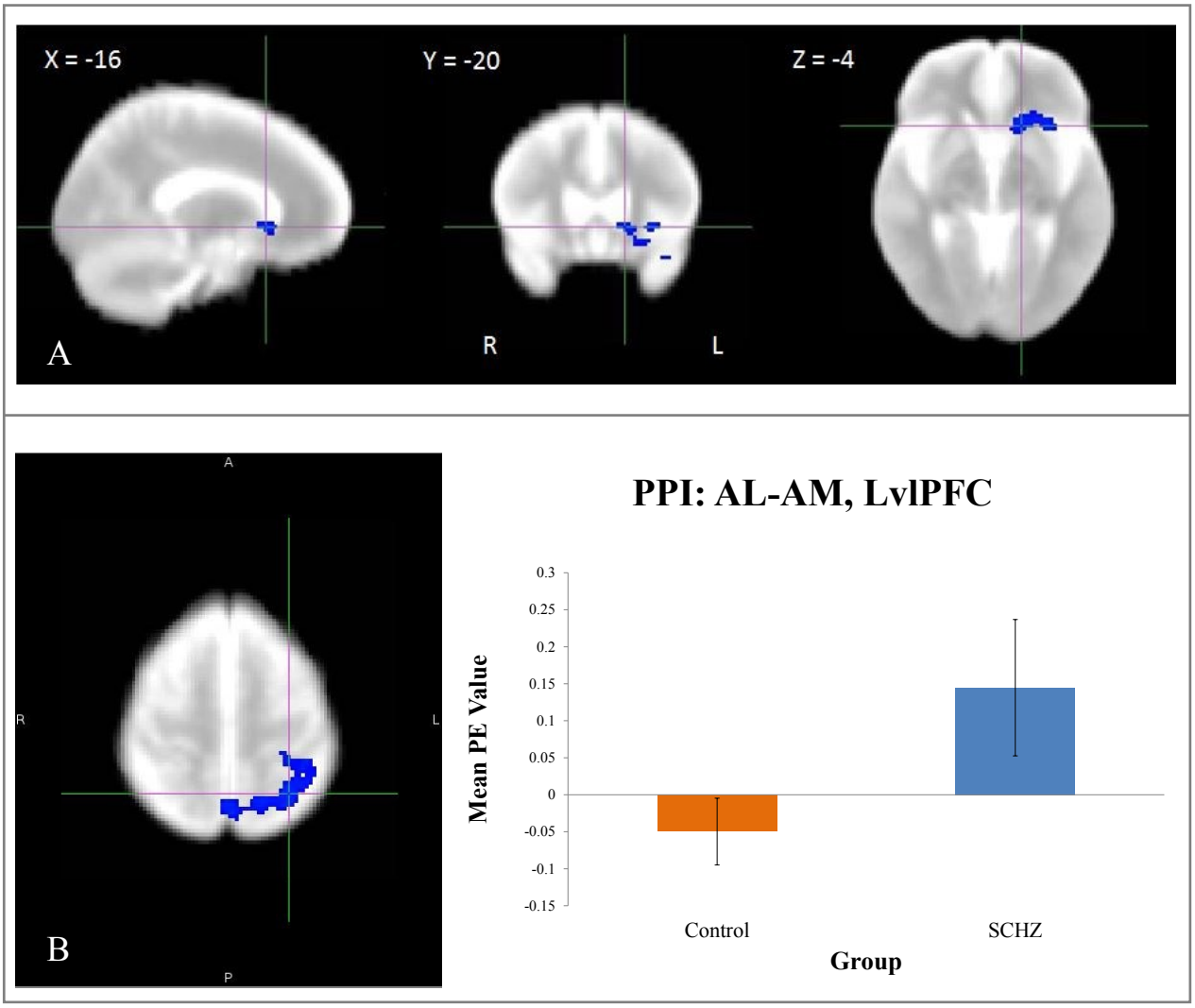
Red = Control>BD patients, Blue = Control > SCZ patients, Green = Controls >Patients.

Figure 4. fMRI activations during *Affect-Label>Gender-Label* contrast.



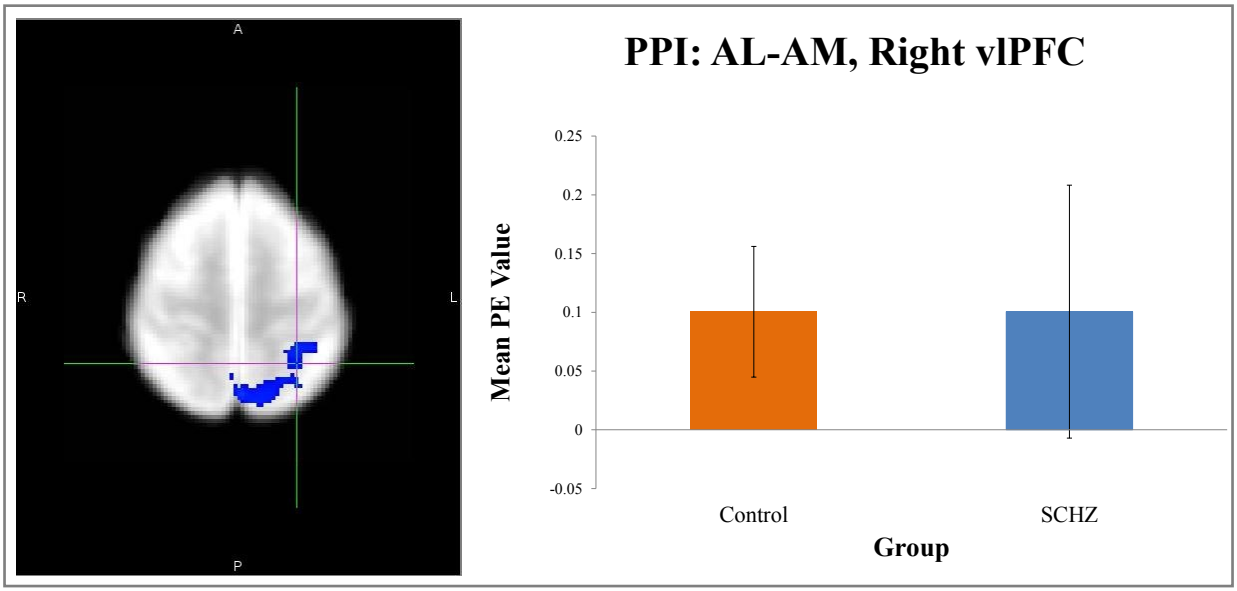
A. Yellow = Controls; Blue = SCZ patients.
B. Dark blue = SCZ>Controls; Light blue = SCZ>BD patients

Figure 5.



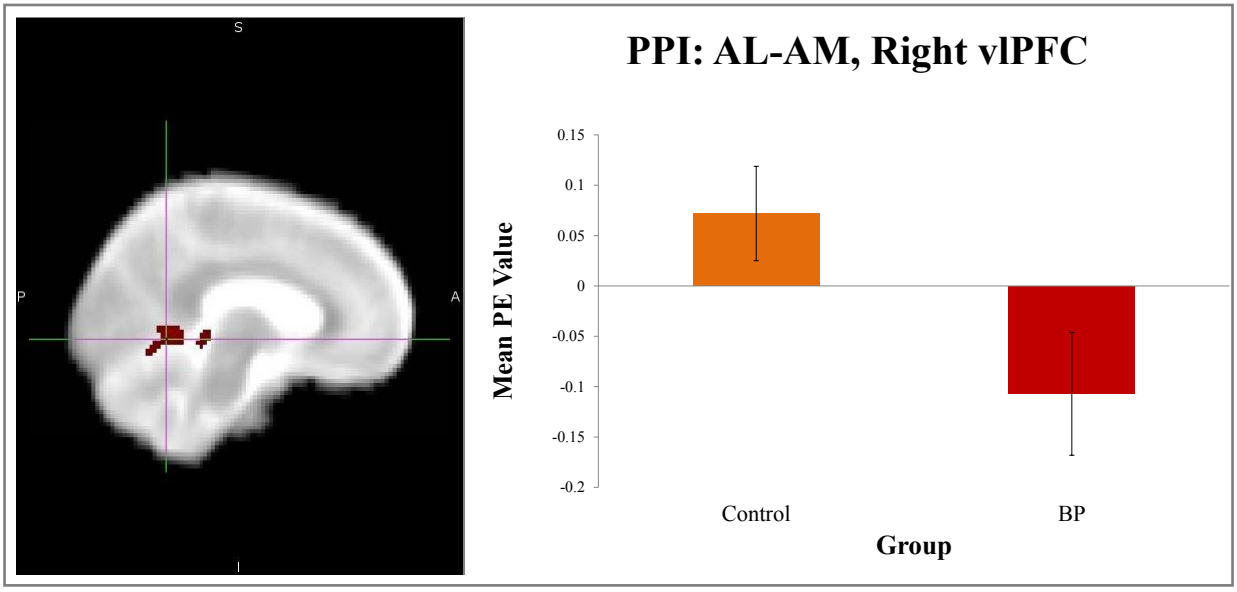
A. Regions of significant psychophysiological interaction between *AL-AM* and activity of the left ventrolateral prefrontal cortex in schizophrenia patients only (left caudate and insula).
B. Region of significant group difference (left superior parietal lobule, precuneus, supramarginal gyrus, lateral occipital cortex; axial slice shown at MNI coordinate: -32, -58, 54) in PPI between the *AL-AM* contrast and activity of the left ventrolateral prefrontal cortex.

Figure 6.



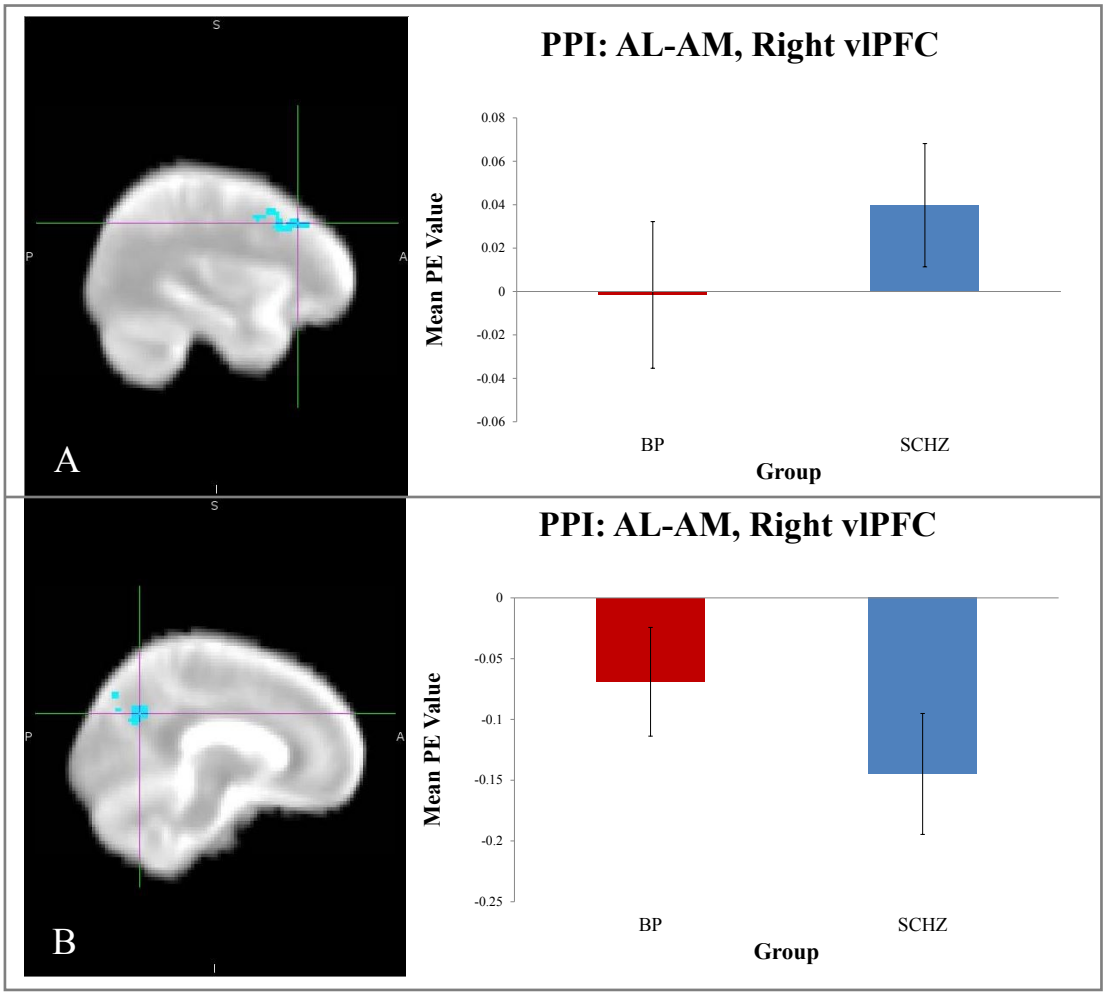
Region of significant group difference (left superior parietal lobule, precuneus, supramarginal gyrus, lateral occipital cortex; axial slice shown at MNI coordinate: -30, -52, 56) in PPI between the *AL-AM* contrast and activity of the right ventrolateral prefrontal cortex.

Figure 7.



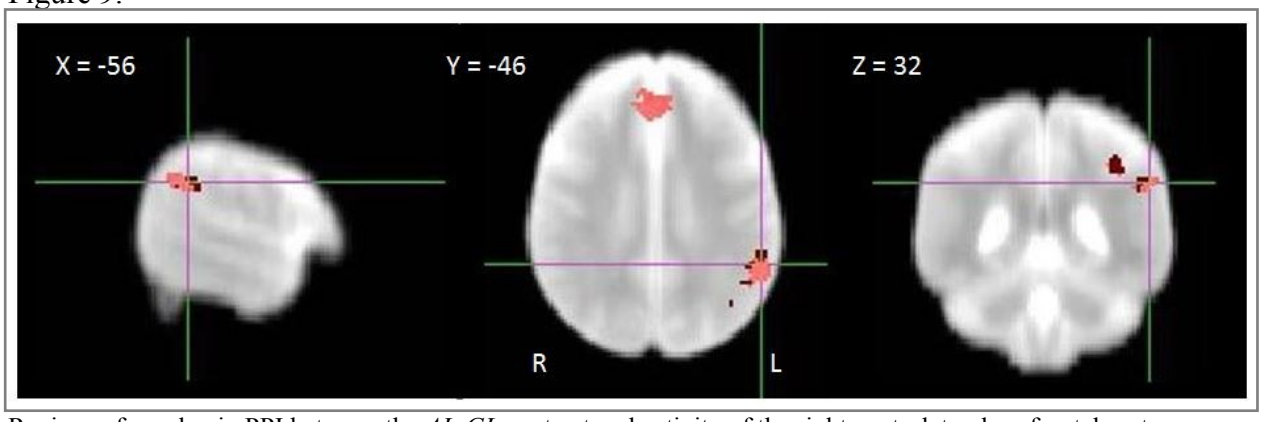
Region of significant group difference (anterior lingual gyrus/ventral precuneus; sagittal slice shown at MNI coordinate: -8, -56, -4) in PPI between the *AL-AM* contrast and activity of the right ventrolateral prefrontal cortex.

Figure 8.



Regions of significant group difference (A: left middle frontal gyrus, left pre-central gyrus; sagittal slice shown at MNI coordinate: -34, 30, 38. B: precuneus; sagittal slice shown at MNI coordinate: -10, -64, 32) in PPI between the *AL-AM* contrast and activity of the right ventrolateral prefrontal cortex.

Figure 9.



Regions of overlap in PPI between the *AL-GL* contrast and activity of the right ventrolateral prefrontal cortex across all groups.

Figure 10. Positive and Negative Symptomatology with Left and Right Amygdala by Patient Group

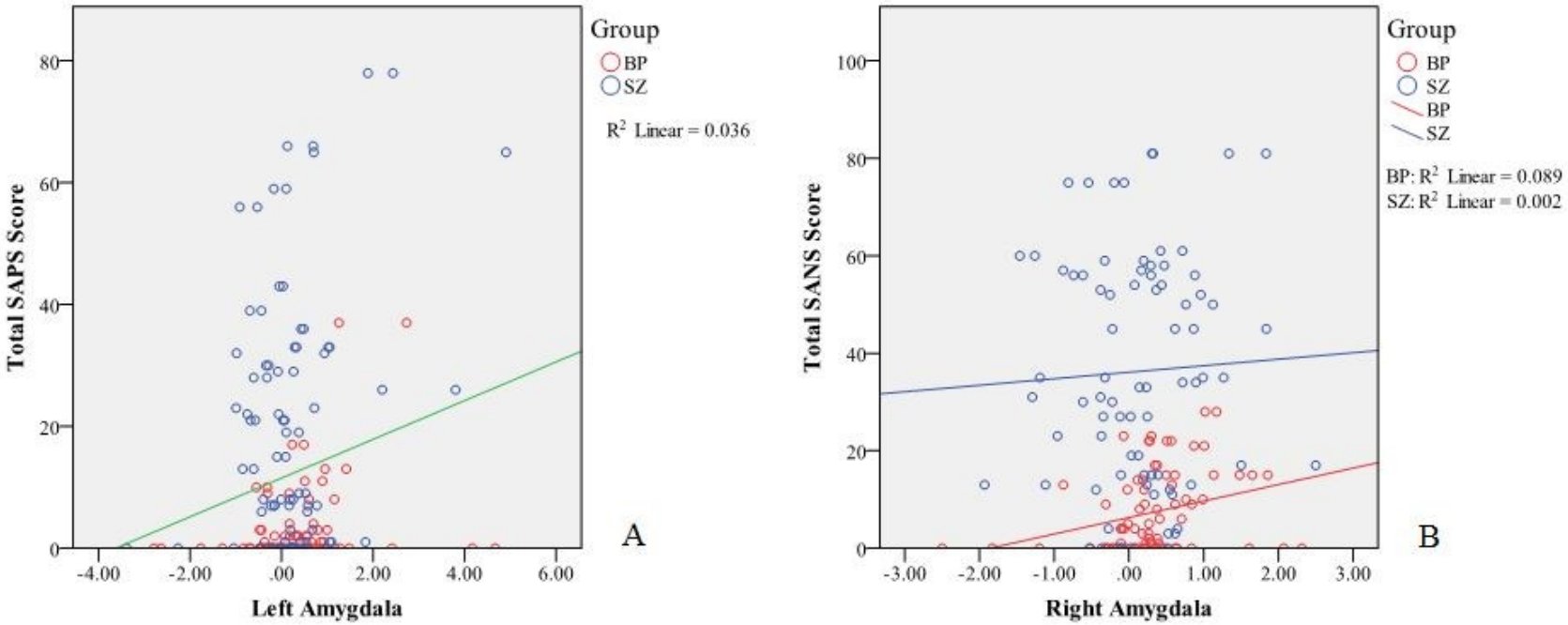
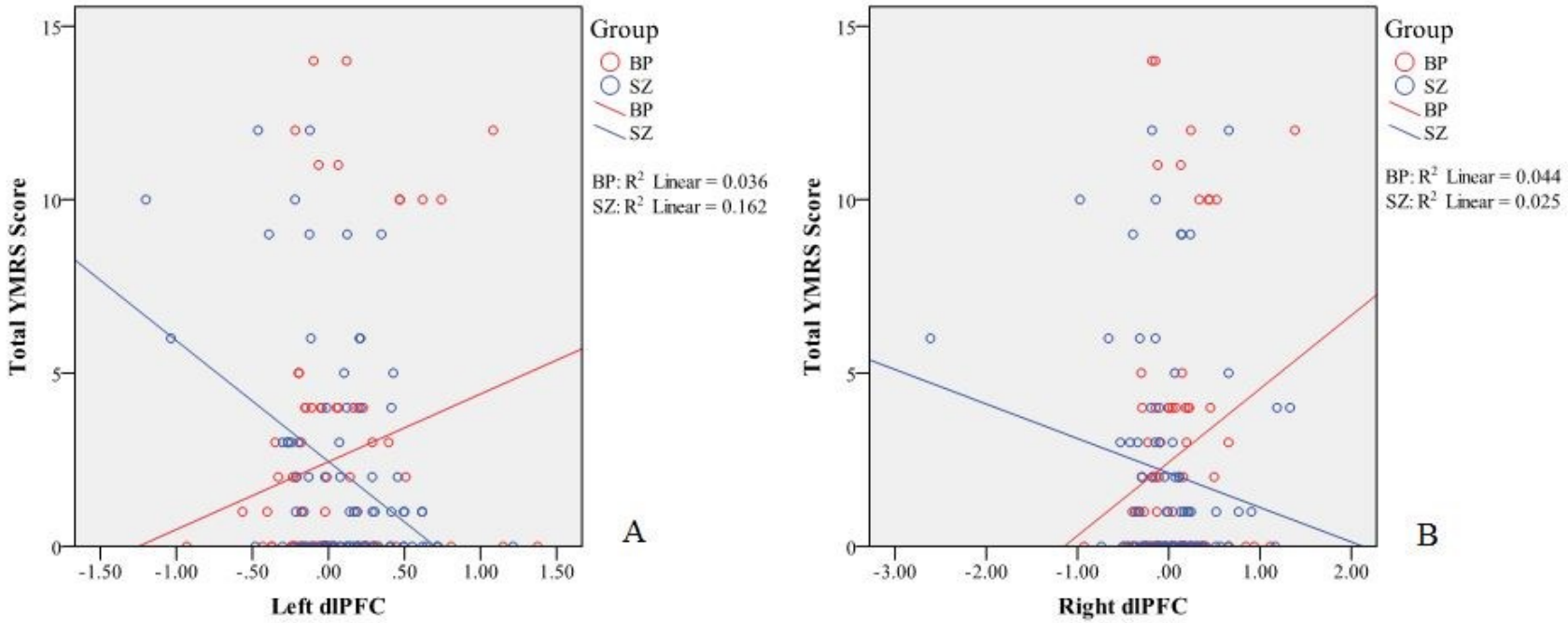


Figure 11. Mania Symptomatology with Left and Right dlPFC by Patient Group



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