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Brain Mapping Biomarkers of Socio-Emotional Processing in Schizophrenia

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The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative has formed with the expressed intent of identifying constructs and paradigms that would identify biomarkers of psychosis. The manipulation of these biomarkers would serve as targets for treatment interventions. The second phase of CNTRICS consisted of critical discussions evaluating brain mapping (functional neuroimaging and brain electrical activity) paradigms as biomarkers to measure specific constructs. Among the constructs identified in, CNTRICS I was socio-emotional processing, specifically focused on affect recognition. Here, we provide a critical appraisal of the ability of candidate socio-emotional tasks to identify putative biomarkers and recommendations for future directions in this rapidly moving research domain.

Key words: emotion/social/fMRI/ERP/amygdala

Introduction

While the earliest conceptualizations of schizophrenia emphasized the importance of social and emotional deficits, only in the last 2 decades have the tools become available to study these impairments. The broad concept of negative symptoms has highlighted impairments in emotional expression as well as hedonic capacity and socialization, and these deficits are well-known predictors of poor outcome. Investigators have also come to appreciate the role of social cognitive deficits, also predicting poor outcome, independent of negative symptoms, and more general cognitive deficits. Finally, more recent research has focused on another side of emotional deficits, reflecting, in part, the observation that patients with schizophrenia experience emotions, particularly negative ones, more than healthy subjects and more than would be expected from their reduced affective expressivity. Negative emotions and dysregulated affective states are prominent features of the clinical phenotype, often appearing in prodromal stages of the disorder. Together, social and emotional disturbances are major features of schizophrenia and an important target for interventions.

Recognizing the importance of socio-emotional processing in schizophrenia, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative has identified socio-emotional processing as one of the domains for development of translational research programs and biomarkers of treatment response. At the first CNTRICS I meeting in 2007, a group of experts surveyed the field of social cognitive and affective neuroscience to identify a set of constructs that characterized the type of investigations carried out in this area.[1] While social and emotional processes are often seen as separate domains of research, with distinct meetings, journals, and professional groups, the overlap between methods and identified neurocircuits makes it difficult to truly separate these domains; hence, the joining of the 2 areas in a single domain for these purposes. From this initial meeting, 5 constructs were used to delineate the domains of social cognitive and affective neuroscience: (1) acquisition of social-affective values and responses, (2) recognizing and responding to socio-emotional stimuli, (3) embodied simulation or low-level mental state inference, (4) high-level mental state-trait inference, and (5) context-sensitive regulation.

The 5 constructs constitute a preliminary roadmap of inquiry, establishing a framework to characterize socio-emotional dysfunction in schizophrenia. Construct 1, describing processes by which the initial socio-emotional responses are acquired, as in fear conditioning or reward learning, was felt to be closer to the CNTRICS domain of long-term memory. Hence, for the sake of parsimony, these paradigms will not be further discussed here (a discussion of the learning and long-term memory paradigms from CNTRICS II are covered elsewhere in this issue). Constructs 3, 4, and 5 represent areas of active investigation; however, at the time of CNTRICS I, these 3 constructs required more study in healthy brains before

they could drive translational research programs. Only construct 2—recognizing and responding to socio-emotional stimuli—was felt by the experts contributing to the CNTRICS process to be ready for translation.

Within this construct, investigators have identified systems in the amygdala, ventral prefrontal cortex, insula, fusiform face area, and the superior temporal cortex, involved in recognizing emotional expressions in faces, body postures, as well as the experience of emotion and value. Many of the neural systems that process face stimuli also process the emotional qualities of faces, although nonemotional qualities, eg, identity, do exhibit dissociable processing. Face stimuli are initially processed in the fusiform face area and lateral occipital cortex, possibly corresponding to an electrophysiological component that occurs around 170 ms after stimulus onset. Although primarily concerned with invariant structural features of the face, these early processing areas are modulated by emotional expression, particularly of fear. The amygdala contains face-sensitive cells, and it shows enhanced responses to emotionally salient faces. It sends feedback to visual processing areas, which appear to modulate the processing of emotional faces. Other areas implicated in processing emotional faces include the superior temporal sulcus, somatosensory cortex, thalamus, anterior cingulate gyrus, and medial frontal cortex. Specific emotions have been associated with nodes of face processing regions, such as disgust in the insula and fear in the amygdala, although it is also the case that a distributed network is involved in processing all facial expressions. For recent reviews of face emotion processing, see ref.[2,3]

Considering that significant work has transpired since CNTRICS I, it is important to keep in mind that the socio-emotional constructs were selected to stimulate research and, ultimately, generate better frameworks for understanding brain function and dysfunction. They have guided the selection of specific paradigms that might serve as biomarkers, although they need to be regarded as preliminary formulations reflecting the current state of research. For a complete description of the CNTRICS task nomination and selection process, see ref.,[4] as well as the accompanying overview article in this volume.

At the third meeting of CNTRICS II, in October 2011, 5 paradigms, nominated by web-based survey, were evaluated (see table 1 for a summary of the evaluations obtained at the meeting). The goal of this article is to report the discussion from that meeting, providing a critical analysis of these tasks, specifically because they might be developed into biomarkers. From CNTRICS I, the Penn Emotion Recognition paradigm was recommended for further development.[5] The other 4 tasks, none of which were previously recommended, will be discussed more succinctly. Finally, we will briefly discuss some of the recent developments in socio-emotional research relevant for biomarker development. Overall, the intention of the article is to provide an overview of the CNTRICS process in search of socio-emotional biomarkers, particularly for schizophrenia researchers not familiar with these areas.

Facial Affect Perception: Penn Emotion Recognition Task

Emotional faces, such as those developed by Ekman, have been the most popular stimuli used to elicit and study emotion, which is not surprising given the rich nuanced communication channel provided by the human face. A perusal of the published literature (as of March 2011) reveals close to 40 studies in schizophrenia research using face stimuli and positron emission tomography or functional magnetic resonance imaging (fMRI) and over 1 dozen with electroencephalography or magnetoencephalography (MEG). The Penn Emotion Recognition task has been used both with fMRI [6,7] and with event-related potentials.[8] The Penn face stimuli were generated both in posed and in evoked emotions using professional actors, and extensive validation studies have established the accuracy of the emotional expressions (fear, anger, sadness, happiness, and neutral).[9] In the fMRI studies of the task, individuals view a face and choose the correct label for the evoked (felt) emotion. In some variations, a control task provides implicit stimulus exposure to subjects who judge the gender or age of the face. See figure 1 for an example of stimuli from this task. Among the paradigms discussed at the CNTRICS meeting, the Penn Emotion Recognition task was felt to possess the strongest track record for validity and reliability for activating neurocircuits, with important caveats, discussed below.

Considering the relative strength of the knowledge about the neurocircuitry of emotional face perception, these tasks provide promising paradigms for assessing neural correlates of the construct, although many issues remain to be addressed. The Penn Emotion Recognition task performs, as well as other tasks in eliciting activity in target regions, both in fMRI[10] and in event-related potential (ERP)[8] studies. However, neuroimaging studies of face processing in schizophrenia have employed a variety of contrasts to elicit activity, eg, passive presentation of faces, judgment of gender, or judgment of emotional valence, as in the Penn Emotion task. As can be seen in table 2, there is a large parameter space for face emotion tasks, and this table does not include contextual manipulations of face processing, eg, 'This person just won $500' (see below). Uncertainty about how these parameters affect neural activity limits the validity and reliability of face emotion tasks. For example, whether subjects attend to the emotional characteristics of a face explicitly (eg, labeling an emotion) or only implicitly process emotional content (eg, judging gender) can affect the recruitment of neural circuitry. Some work shows that the act of labeling face emotion reduces amygdala activity compared with passive viewing,[11] while a recent meta-analysis suggests that explicit processing of emotional faces is

Table 1. Summary of the Expert Evaluations of Socio-Emotional Tasks Nominated in Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) Initiative

Paradigm	Valid Measure of Neural Systems	Reliable Measure of Neural Systems	Measures Necessary Function of Systems	Relationship Between Individual Differences and Performance	Sensitivity to Manipulation	Link to Functional Outcome	Link to Neural Dysfunction	Psychometric Properties	Neurometric Properties	Practicality and Tolerability
Penn emotion recognition (fMRI and ERP)	++	++	+	++	+	?	++	+	?	+++
Reading the mind in the eyes (fMRI)	+	+	+	+	?	?	+	?	?	++
Bubbles task (MEG)	++	++	+	+	?	?	?	?	?	+
Emotional light walkers (fMRI)	++	++	+	+	?	?	?	?	?	++
Faces in context (fMRI)	+	+	+	+	?	?	?	?	?	++

Note: Key: ?, no information; +, weak; ++, moderate; +++, strong.

generally associated with a greater signal in the amygdala and the fusiform gyrus.[2] This uncertainty about how task instructions affect signal activation, along with the fact that individuals adopt different strategies, raises concerns around reliability, and no published data speak to BOLD signal reliability in the Penn Emotion task. Other issues, such as the role of labeling versus matching the emotion or the duration of face stimulus presentation, have poorly understood effects on neural activity. Thus, specific paradigms, such as the Penn Emotion task, may evoke activity in ways that do not generalize across seemingly similar paradigms.

Linking behavior with neural activity is an important characteristic of a robust biomarker. In behavioral tests, patients with schizophrenia show impairments in the ability to label facial affect,[12] related to functional outcome,[13] although it has still not been established whether or not the deficit in face emotion processing reflects more generalized perceptual or cognitive dysfunction.[14] This uncertainty about the exact nature of the behavioral deficit complicates the ability to map behavioral parameters to specific neural circuits. Nevertheless, correlations with specific symptoms may provide important linkages. With the Penn Emotion Recognition task, Gur and colleagues[6] demonstrated that greater amygdala activation was associated with more correct responses to angry and fearful faces in controls, whereas patients with schizophrenia had a greater signal to incorrect identifications of threat-related faces. These early results suggest that individual differences in the response to emotional stimuli may be mapped onto the circuitry elicited by face processing, but much more work will be needed to make definitive statements.

A useful biomarker should have the capacity to measure psychotherapeutic or pharmacologic manipulations, but so far, little published work is available. A recent study by Habel and colleagues,[15] using the Penn task face set, found that schizophrenia patients showed increased fMRI BOLD signal in occipital and parietal cortex after affect recognition training. In patients with depression who have undergone tryptophan depletion, reduction in mood was associated with greater activity in the right amygdala in response to fearful faces (compared with happy faces), as well as decreased accuracy.[16] Work in healthy individuals has shown that emotional face perception was also modulated by acute tryptophan depletion,[17] and amygdala activation has been reduced by selective serotonin uptake blockade,[18] cannabinoids,[19] and benzodiazepines.[20] While none of this pharmacologic work has been published in schizophrenia patients, the data suggest that these paradigms may serve as biomarkers for understanding mechanisms of treatment relevant to psychosis.

Brain mapping studies from the published literature have begun to establish a picture of socio-emotional neurocircuit dysfunction in schizophrenia, although caution is

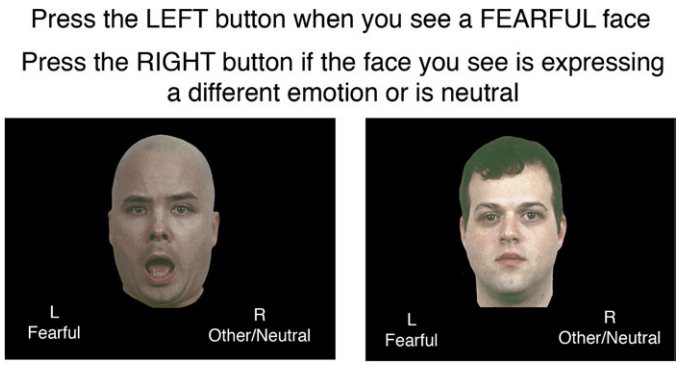

Fig. 1. The figure shows sample stimuli from the Penn Emotion Recognition task, derived from Gur et al. (2007)[6] and Gur et al. (2002)[7] with permission. The task is a hybrid design, with 4, 90-second blocks presented in which a subject must identify whether a target emotion, eg, fear, is present. If present, a subject presses a button (here, on the left). For neutral expressions and foil emotions, eg, happy and sad, the other button (on the right) is pressed. Face stimuli are presented for 3 seconds within each block, separated by 24 seconds of rest, when scrambled, unidentifiable images. Four runs are presented, each targeting a specific emotional expression (fearful, angry, happy, and sad).

Table 2. Experimental Parameters in Face Emotion Processing

Parameter	Values
Face stimuli	
Expressions	Basic: fear, anger, happy, sad, disgust, surprise, neutral; complex/ambiguous
Intensity	Fixed, variable (morphed from neutral, eg, 50%–150% sad)
Stimulus set	Validated, generated de novo
Emotion evocation	Posed, naturally evoked
Face details	Cropped, with hair, schematic
Dynamics	Static expressions, dynamic expressions
Face orientation	Full face, looking away
Gaze	Forward, deviated
Presentation	
Duration	Supraliminal, subliminal (with mask)
Configuration	Single face, triplets (for matching/ labeling)
Trial grouping	Blocked, event-related, hybrid
Response	During face stimuli, after stimuli
Task	
Instruction set	No task (passive);Implicit (attention not directed at face emotion): judge gender, judge face attribute (eg, nose width), judge nonemotional personal characteristic (eg, age range);*Explicit (attention directed to face emotion):* identify basic emotion, judge character (eg, trustworthiness, likability)
Response set	Fixed forced choice (binary vs multiple), match to exemplar

needed in interpreting these results. A recent meta-analysis of 17 studies with emotional faces found that healthy subjects activated the bilateral parahippocampal gyrus/amygdala region, right superior frontal gyrus, right lentiform nucleus, and bilateral fusiform gyri greater than schizophrenic patients.[21] No activation clusters were reported where patients exceeded controls. Another meta-analytic study examined 35 reports using face stimuli, in addition to olfactory, auditory, and visual stimuli, focused strictly on effect sizes of amygdala change.[22] This analysis also found underactivation of the amygdala in schizophrenia (a mean effect size of 0.20) but only for contrasts between emotional and neutral faces. When activity to emotional faces alone was examined, there were no group differences. The authors suggested that schizophrenia patients may overactivate amygdala to neutral faces. Increased activity to neutral faces has been noted in the amygdala[23] and increased baseline activity in the amygdala across conditions has also been reported.[24] If patients are prone to misinterpret neutral situations as threatening, this may indeed extend to all task conditions, meaning that contrasts, eg, between fearful and neutral faces, would show ''underactivation.'' Thus, while a failure to differentiate between emotional and neutral faces seems to be a consistent finding in the amygdala/parahippocampal region in schizophrenia, it is not clear if this reflects generalized overactivity of a salience detection circuit or a failure to detect the more salient stimuli, eg, emotional faces.

Considering practical aspects of using emotional face paradigms—psychometric/neurometric properties and tolerability—the Penn Emotion Recognition task, and other face paradigms, has some distinct advantages, as well as areas where more investigation is needed. In general, emotional face recognition tasks earned high marks from the CNTRICS discussions for their ease of administration and straightforward nature. Tasks can be completed with adequate data sampling in ~10 minutes for blocked designs, although event-related designs require at least twice that much time in the scanner. On the other hand, relatively little data exist on the test-retest reliability and floor/ceiling effects, either in the psychological-behavioral realm or in the neuroimaging or ERP signals. Behavioral test-retest reliability is in the range of 0.76–0.80 for patients and controls, and accuracy is in the range of 73–84%.[5] However, neurometric data, eg, reliability of BOLD signal change, do not exist.

To summarize, the status of emotion face recognition in general, and the Penn Emotion Recognition task in particular, as a biomarker is promising but in need of further development. The strengths of these paradigms include a relatively well-understood neural pathway, along with the ease of task administration and data showing susceptibility to behavioral training and pharmacologic manipulation. On the other hand, effect sizes for paradigms designed for amygdala activation appear relatively small, and issues around performance (differences in strategy, eye movements) are generally not monitored.

Furthermore, uncertainty about how experimental parameters affect neural signal, along with a dearth of information on reliability, effect size and variance, limits the utility of these tasks as biomarkers at this time. While it is likely that specific tasks, such as the Penn Emotion Recognition task, can be optimized to provide stronger effect sizes, the absence of the necessary psychometric/neurometric validation prevents the employ of these tasks as potential biomarkers, at this stage of research. Nevertheless, additional development is worthwhile.

Other Nominated Tasks

There were 4 other nominated tasks in this category that received equal discussion at the meeting, although with less data, less will be said of them here. Like the Penn Emotion Recognition task, they were considered to be in the preliminary stages of development as biomarkers, but as table 1 shows, information necessary to evaluate the status of these paradigms as biomarkers is mostly unknown. At the same time, they represent a number of useful leads that may provide the basis for future biomarkers.

One nominated paradigm was adopted from the autism literature: reading the mind in the eyes.[25] Similar to facial emotion recognition tasks, this task measures the ability to report which of 4 words best describes the thoughts or feelings of a person, using only a photograph of the person's eyes. One of the putative advantages of using only the eyes in an emotion recognition task is that while the eyes are emotionally salient, an impoverished stimulus constrains the number of strategies for the task and therefore the number of wrong strategies. In this task, photographs of eyes are presented at the center of the screen, along with 4 adjectives at the bottom of the screen, one of which is the correct response. Behavioral analyses focus on both accuracy and reaction time, as measured by a voice key. The test has shown convergent validity with theory of mind tests and has been shown to differentiate individuals with autism spectrum disorders[26] and lesions of the amygdala[27] from controls. Patients with schizophrenia perform worse than healthy control subjects,[28] as do their nonn-ill first-degree relatives.[29] In 1 fMRI study, the contrasts of reading the mind in the eyes versus gender discrimination showed, among other regions, activations in a socio-emotional network consisting of medial prefrontal cortex, inferior prefrontal cortex, superior temporal gyrus, and amygdala.[30] The committee thought that the relative strengths of the task were its potential to identify the neural system reliably recruited by the construct and that it appeared to have good practicality and tolerability. However, the task has a significant verbal processing load, raising questions about specificity for socio-emotional dysfunction in schizophrenia. It also faces many of the other challenges of emotion recognition tasks outlined above.

The committee was more enthusiastic about approaches adopted in the remaining 3 paradigms, even these paradigms appeared in the early phases of development. In these tasks, difficulty or stimulus qualities are varied systematically (sometimes referred to as 'parametric' tasks). The first of these paradigms was a third emotion recognition task, known as the Bubbles task.[31,32] In this task, rather than a full picture of an emotional face or the eyes of an emotional face, participants are presented with a subsample of the face, formed by masking all the face except for a random "bubble" with a circularly symmetric Gaussian aperture. While 1 such bubble is typically too little to correctly classify the face, 9 such bubbles, covering different parts of the face, provide 70%–75% categorization accuracy for either the emotional expression or the gender of the underlying face.[32] After many individual trials, the paradigm generates a map of the facial features correlated with correct classifications, independently for each subject, thereby showing which features a subject used to make classifications. This information can be used, for example, to demonstrate that whereas most individuals focus on information from the eyes when making affect recognition judgments, patients with damage to the amygdala do not.[33] In 1 MEG study by Smith and colleagues,[32] experimenters identified where specific features were processed in isolation across occipital extrastriate regions and then later aggregated in occipitotemporal regions. The task and MEG method also allowed the time course of these processes to be carefully parsed.

The committee thought that the relative strength of the task was its capacity to provide a psychometric function for participants' use of emotionally salient cues. In preliminary work, patients with schizophrenia required more bubbles, and therefore more facial information, to make correct classifications.[34] Although it is unclear how much this task taps perceptual or even cognitive memory systems to build an identifiable percept of a specific face emotion, schizophrenia patients appeared to use different regions of the face to identify an emotion,[34] suggesting that a generalized deficit cannot account for all the abnormal performance in the task. The bubbles task is still in the early phases of development in schizophrenia research, and the large number of trials required to map salient face regions remains a major obstacle. Thus, it scored low on its apparent tolerability and practicality. For example, for Lee and colleagues,[34] each experimental session required 1 hour, and the study in healthy subjects by Smith and colleagues required 4000 trials. However, the extent to which the task necessarily would last this long was not clear, although this analysis could likely be done with extant data.

The second parametric task was the "Emotional Point-light Walker" paradigm developed by Heberlein and colleagues,[35] based on the work of Johansson.[36] Johansson observed that even an impoverished portrayal of biological movement, as when an actor fit with small lights

attached to his body was filmed while moving in the dark, could express recognizable emotional states. In principle, such movement could either come from movements of the body or come from face. In such a study, a stimulus set might consist of clips illustrating biological movement via point-light walkers expressing 1 of 5 emotional states (fear, anger, happiness, sadness, or neutral) that the participant would be required to identify. Accuracy and reaction time could then be collected for each clip. Using such a procedure to depict facial movements, Tomlinson and colleagues[37] demonstrated that individuals with schizophrenia perceive emotion from point lights more easily than from static images. A network of brain regions has been associated with perception of biological motion using this procedure with fMRI, including the superior temporal sulcus/gyrus, posterior inferior temporal gyrus, fusiform gyrus, amygdala, the inferior prefrontal cortex, and the premotor frontal regions.[38] The committee found this to be an interesting manipulation that could be used in a parametric manner to develop a psychometric function. However, the evidence for a lack of a patient impairment in the task (perception of the emotions within biological movement appeared to be relatively spared), and the broader sense that the task was still in its early phases of development dampened enthusiasm.

The last paradigm the committee considered was Faces in Context, also referred to as the "vignette-face" task.[39] This paradigm, for which there is no standard task per se, involves comparing affect recognition in the case where a face is presented in isolation (ie, alone, as per most affect recognition paradigms) vs contextually constrained (ie, face presented with a cognitive frame, eg, a surprised face after being told she won $500 compared with being told she lost $500). The insight underlying this manipulation is that our interpretations of facial emotions rarely occur in isolation (as required in other affect recognition tasks) and are frequently constrained by the circumstances. Of course, this insight can be applied broadly to a wide variety of disambiguating social stimuli. Green and colleagues[40] have demonstrated that patients with schizophrenia fail to use context to constrain their affective interpretations, particularly when the contextual cues suggested a complex emotional state with a negative valence (eg, anger, fear, sadness). Kim and colleagues[41] demonstrated the capacity for this task to activate the cortico-amygdalar networks associated with resolving ambiguous emotional stimuli. To our knowledge, no neuroimaging work using this paradigm has been done in schizophrenia patients. Like the previous 2 parametric tests, the committee discussion was supportive of this manipulation and felt that its relative strengths were its capacity to identify important neural systems and its potential practicality and tolerability. There was a hope that future versions might include manipulations that would increase the interpretability of the behavioral data and that there would be an effort to optimize the context manipulation.

Future Directions

Research into the brain basis of social and emotional functions has moved at a rapid pace in the last 5 years, and psychosis research is now poised to take advantage of more sophisticated paradigms. In this section, we will briefly review a few potential areas of study relevant for promising biomarkers. In keeping with the CNTRICS roadmap, we will not delve into the promising work being done in reward processing and neuroeconomics, although it is worth mentioning that this area of inquiry may provide insight into negative symptoms of schizophrenics.

Much activity and interest have been generated by theory of mind paradigms, referring to the ability to infer another person's mental states (Construct #4 from CNTRICS I[1]). Given the prima facie evidence that many delusions ascribe false agency to other individuals and that communication impairments mark other symptoms, theory of mind may be a useful domain to examine for specific deficits. Theory of mind paradigms, often more generally referred to as "mentalizing," typically involve stories in pictures or text that show how someone came to have a false belief or utilize indirect speech, eg, "hinting." There is a rich literature on the formation of such false beliefs in both comparative (non-human primate) and developmental psychology literatures, and theory of mind has been found to be impaired in patients with autism.[42] In schizophrenia, work in this domain began about 15 years ago[43] and has expanded significantly, as documented in recent reviews, eg., ref.[44] These reviews suggest a large effect size (Cohen's $d = 0.90–1.08$) associated with patients' impairment on mentalizing tasks, greatest in patients with disorganization, although this impairment has not been completely disentangled from a generalized intellectual deficit. Brain mapping studies of mentalizing have implicated paracingulate gyrus/dorsal medial prefrontal cortex (PFC), precuneus, temporal-parietal junction, superior temporal sulcus, and temporal poles in healthy subjects.[45,46] Several neuroimaging studies have been published in schizophrenia patients (see online supplementary material table S2), which tend to show reduced activity in this network. Perhaps most importantly, some of the nodes recruited by mentalizing tasks, such as the precuneus and dorsal medial PFC, are not activated by cognitive tasks; thus, theory of mind paradigms may tap distinct systems of socio-emotional processing and certainly have the potential for producing future biomarkers.

Potential biomarkers of socio-emotional processing described so far have generally avoided emotional experience, per se, although abnormal affects, such as anxiety and depression, are important facets of the schizophrenia phenotype. A somewhat paradoxical finding has been the preserved ability to appraise "in-the-moment" emotional experience in spite of obvious reductions in emotional expression.[47] On the other hand, the ability to anticipate or

recall emotional experience is diminished, as revealed by standard assays of hedonic capacity. One recent study found that after experiencing emotional stimuli (positive and negative), schizophrenia patients showed reduced activity of the dorsolateral PFC when they had to maintain a representation of that experience, a reduction that correlated with the severity of their anhedonia.[48] A related area of investigation could explore reappraisal tasks that require subjects to reframe their experience of a negative stimulus, a key therapeutic process in cognitive behavioral therapy. Performance could be measured via change in subjective ratings or objectively through a change in electrophysiological components.[49] Issues around the transparent demand characteristics of the task, along with interpretive problems posed by generalized impairments in schizophrenia, need to be addressed, but this type of task could provide a biomarker for treatment response in cognitive behavioral therapy in schizophrenia.

Affective neuroscience research has also examined cognitive-emotional interactions, and this area has been well explored in anxiety and depressive disorders.[50] To date, a few studies have examined cognitive-emotional interactions in schizophrenia (see online supplementary material table S3), but research has not utilized comparison groups of anxiety patients to discern common and distinct mechanisms of emotional processing. A recent study of schizophrenia patients performing an oddball task in which they had to ignore salient emotional pictures showed reduced activity in similar regions involved in emotional regulation, including the anterior cingulate cortex and right inferior frontal gyrus activation (see online supplementary materialtable S3), regions frequently implicated in patients with anxiety disorders. In line with the research domain criteria (RDoC) of the National Institute of Mental Health, convergent studies of emotion in schizophrenia might do well to find common and distinct mechanisms of emotional dysfunction in schizophrenia and anxiety/affective disorders.

Conclusions

The search for biomarkers of psychiatric illness remains the holy grail of biological psychiatry. Considerable advances have been made in our understanding of the basic neural systems involved in social and emotional processing, although we still lack a sufficiently advanced model of brain mechanisms that would successfully guide the development of new therapies. The CNTRICS process has helped to channel the attention of researchers to find viable constructs to guide the treatment development research in general and more specifically toward domains such as socio-emotional processing. The paradigms discussed above provide promising beginnings but not yet mature biomarkers ready for deployment in the setting of treatment trials. However, given the importance of socio-emotional dysfunction in schizophrenia, and the progress to date, further development of this domain is critical for discovering better treatments for schizophrenia.

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Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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