Meta-Analysis of Functional Neuroimaging Studies of Emotion Perception and Experience in Schizophrenia

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Background: Neuroimaging studies of emotion in schizophrenia have reported abnormalities in amygdala and other regions, although divergent results and heterogeneous paradigms complicate conclusions from single experiments. To identify more consistent patterns of dysfunction, a meta-analysis of functional imaging studies of emotion was undertaken.

Methods: Searching Medline and PsycINFO databases through January 2011, 88 potential articles were identified, of which 26 met inclusion criteria, comprising 450 patients with schizophrenia and 422 healthy comparison subjects. Contrasts were selected to include emotion perception and emotion experience. Foci from individual studies were subjected to a voxelwise meta-analysis using multilevel kernel density analysis.

Results: For emotional experience, comparison subjects showed greater activation in the left occipital pole. For emotional perception, schizophrenia subjects showed reduced activation in bilateral amygdala, visual processing areas, anterior cingulate cortex, dorsolateral frontal cortex, medial frontal cortex, and subcortical structures. Schizophrenia subjects showed greater activation in the cuneus, parietal lobule, precentral gyrus, and superior temporal gyrus. Combining across studies and eliminating studies that did not balance on effort and stimulus complexity eliminated most differences in visual processing regions as well as most areas where schizophrenia subjects showed a greater signal. Reduced reactivity of the amygdala appeared primarily in implicit studies of emotion, whereas deficits in anterior cingulate cortex activity appeared throughout all contrasts.

Conclusions: Processing emotional stimuli, schizophrenia patients show reduced activation in areas engaged by emotional stimuli, although in some conditions, schizophrenia patients exhibit increased activation in areas outside those traditionally associated with emotion, possibly representing compensatory processing.

Key Words: Amygdala, anterior cingulate cortex, functional magnetic resonance imaging, medial frontal cortex, occipital cortex, positron emission tomography

Emotional disturbances in schizophrenia affect a diverse set of processes, including altered emotional expressivity (1), decreased anticipation of hedonic events (1), increased trait negative affect (2), impaired perception of socioemotional signals (3,4), and increased experience of negative emotions (5,6). Other emotional functions, such as the ability to appraise the valence of emotional stimuli, appear relatively intact in schizophrenia (7). Understanding the neural mechanism of affective pathology is an important step toward improving treatment because socioemotional perceptual deficits (8,9) and negative emotions (2) have been associated with poor outcome, independent of positive symptoms and neurocognitive impairment.

Neural structures involved in emotion processing, particularly the amygdala, have been an active subject of neuroimaging research in schizophrenia. Findings with various paradigms and from different laboratories have reported a variety of results, from reduced (10–14) to increased reactivity (15–17) to emotional stimuli. To make sense of these disparate findings, meta-analyses have recently appeared. Li and colleagues (18) used activation likelihood estimation (ALE) to examine 15 studies of face emotion processing in schizophrenia. ALE is a voxel-based meta-analytic technique for examining the spatial distribution of activation foci reported across studies, comparing that distribution to a random distribution, and determining where clusters of foci exceed a chance distribution (19). Li and colleagues found that patients with schizophrenia underactivated the amygdala. In a meta-analysis focused only on amygdala effect sizes in 35 neuroimaging studies, Anticevic and colleagues (20) found reduced reactivity in contrasts between negative and neutral stimuli (including more than just face stimuli), although the effect size (.20 SD) was small. However, they found no difference between patients and control subjects in a direct comparison of amygdala activity for a negative condition. Thus, questions remain about amygdala dysfunction in emotion processing in schizophrenia.

Voxel-based meta-analytic studies, such as ALE, have the advantage of revealing consistent patterns across studies, to confirm tentative conclusions from single studies and generate new hypotheses from unexpected commonalities. Thus, the voxel-based approach can identify regions outside the amygdala that may be relevant for emotion dysfunction in schizophrenia. For example, visual cortex is modulated by emotional visual stimuli (21,22). Other regions implicated in neuroimaging studies of emotion include the superior temporal sulcus, the supramarginal gyrus, dorsomedial prefrontal cortex (dmPFC), anterior cingulate cortex (ACC), orbitofrontal cortex, insula, and subcortical areas (23). Although the study by Li and colleagues identified reduced activity in the fusiform gyrus, right superior frontal gyrus, and lentiform nucleus of schizophrenia patients, four studies (24–27) of the 15 included in their meta-analysis used restricted search regions, focused on the amygdala. The inclusion of coordinates from such studies biases a meta-analysis away from the excluded regions and in favor of the included regions. The ALE-type analysis is based on testing the null hypothesis that foci are randomly distributed throughout the brain. Thus, an unbiased meta-analysis is critical to address the question of which brain regions are implicated in emotion processing deficits

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in schizophrenia. Furthermore, in light of the modest effect size observed by Anticevic and colleagues for the amygdala (20), the findings reported by Li and colleagues (18) may not persist in an unbiased analysis.

In this study, we sought to mine the growing literature on emotion in schizophrenia to generate maps of regions throughout the brain, both in and outside the amygdala. Because emotional processing deficits are many and not all emotional constructs are equally well probed, we confined our analysis to two related processes, emotional experience and emotion perception (28), both of which fall within the construct identified by Ochsner as "recognizing/responding to socio-emotional stimuli" (29). Combining studies within this construct maximized the power to identify common areas of difference. We predicted reduced activation in the amygdala, as well as reduced modulation of visual cortex during emotion perception tasks. In addition to specific predictions, this whole-brain meta-analysis had an exploratory aim to identify other regions of difference. For example, previous meta-analyses of emotion processing have not observed enhanced activity in schizophrenia patients (18, 20), which would constitute an important finding that neural responses to emotional stimuli in schizophrenia are not all characterized by hypoactivity.

Methods and Materials

Study Selection

Medline and PsycINFO databases were searched through January 2011. Search terms included "emotion," "affect," "affective," "emotional," "social perception [MeSH term]," crossed with schizophrenia (as well as variants, including schizoaffective, psychosis) and neuroimaging stems (MRI, magnetic resonance imaging, PET, positron emission tomography). In addition, bibliographies of published studies were also scrutinized. Studies were reviewed and classified by one of the coauthors (IFT, IB, or AH), and then reviewed again by the first author (SFT). Studies of pain were excluded, unless they focused on the anticipation of pain. Studies of reward were not included. Eighty-eight articles were identified that could possibly meet initial inclusion criteria: 1) published in English; 2) included control and patient groups, with statistical comparisons between groups; 3) used PET or functional MRI; 4) used standardized coordinates to locate differential activation via subtraction between tasks ("contrasts"); and 5) conducted unbiased, whole-brain search. Of these 88, 3 did not include stereotactic coordinates, 19 did not include a healthy comparison group, 17 did not use whole-brain coordinates, and 6 were excluded for various reasons (reanalysis of previously published data, analytic technique not comparable in a general linear model framework). Of the 43 remaining articles, we identified 26 (Table 1) that contained specific contrasts, which isolated 1) emotion perception, 2) emotion experience, or 3) a related category of cognitive tasks using emotional stimuli and isolating valence-specific processing. Together, the 26 studies involved 450 patients with schizophrenia and 422 healthy comparison subjects. Except for one (30), all studies included medicated patients or mixed samples of medicated and unmedicated patients. All studies appeared unique, although two by Williams and colleagues (14,31) used the same set of patients in both, studied in separate sessions. Because the comparison subjects were different, we treated these patient-control contrasts as independent of each other.

Contrast Selection

A wide variety of contrasts appear in studies of emotion. To minimize heterogeneity between studies, we focused on emo-

Table 1. Studies Included in Meta-Analysis

	Schizophrenia Subjects				Healthy Comparison Subjects		
Author	Males	Females	Age	Patient Type	Males	Females	Age
Crespo-Facorro *et al.* (76)	16	2	30	Chronic	7	9	29.5
Gur *et al.* (11)	10	4	28.8	Chronic	10	4	27.4
Hempel *et al.* (77)	4	5	26	Chronic	6	4	28
Williams *et al.* (14)	17	10	27.3	Chronic	14	8	27.2
Takahashi *et al.* (78)	10	5	29	Chronic	9	6	29
Johnston *et al.* (12)	8	2	30.6	Chronic	8	2	31.2
Taylor *et al.* (17)	11	7	32	Chronic/first episode	6	4	27
Surguladze *et al.* (16)	15	0	43.1	Chronic	11	0	36.8
Williams *et al.* (31)	17	10	27.3	Chronic	8	5	25.1
Gur *et al.* (66)	12	4	30.1	Chronic	12	5	25
Schneider *et al.* (43)	13	0	32.8	Chronic	26	0	33.4
Pauly *et al.* (30)	12	0	17	First episode	12	0	17
Michalopoulou *et al.* (79)	9	2	35	Chronic	5	4	32
Hall *et al.* (51)	12	7	37.7	Chronic	16	8	35.1
Fakra *et al.* (10)	9	5	37.29	Chronic	9	5	34.65
Seiferth *et al.* (68)	12	0	17.8	First episode	12	0	17.9
Reske *et al.* (80)	10	8	31.94	First episode	10	8	31.94
Kang *et al.* (13)	14	14	29.95	Chronic	14	14	29.9
Kumari *et al.* (32)	13	0	34.5	Chronic	14	0	33.1
Becerril *et al.* (34)	25	13	37	Chronic	21	11	36
Habel *et al.* (35)	14	0	37.14	Chronic	14	0	35.5
Salgado-Pineda *et al.* (81)	9	5	37.3	Chronic	9	5	34.6
Habel *et al.* (67)	15	0	34.4	Chronic	17	0	34.2
Mier *et al.* (50)	11	5	34.25	Chronic	11	5	37
Surguladze *et al.* (33)	17	13	43	Chronic	8	8	40
Holt *et al.* (82)	11	3	43	Chronic	14	4	44
Totals/Averages	326	124	32.5		303	119	31.2