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Abnormal Superior Temporal Connectivity During Fear Perception in Schizophrenia

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Patients with schizophrenia have difficulty in decoding facial affect. A study using event–related functional neuroimaging indicated that errors in fear detection in schizophrenia are associated with paradoxically higher activation in the amygdala and an associated network implicated in threat detection. Furthermore, this exaggerated activation to fearful faces correlated with severity of flat affect. These findings suggest that abnormal threat detection processing may reflect disruptions between nodes that comprise the affective appraisal circuit. Here we examined connectivity within this network by determining the pattern of intercorrelations among brain regions (regions of interest) significantly activated during fear identification in both healthy controls and patients using a novel procedure CORANOVA. This analysis tests differences in the interregional correlation strength between schizophrenia and healthy controls. Healthy subjects' task activation was principally characterized by robust correlations between medial structures like thalamus (THA) and amygdala (AMY) and middle frontal (MF), inferior frontal (IF), and prefrontal cortical (PFC) regions. In contrast, schizophrenia patients displayed no significant correlations between the medial regions and either MF or IF. Further, patients had significantly higher correlations between occipital lingual gyrus and superior temporal gyrus than healthy subjects. These between-group connectivity differences suggest that schizophrenia threat detection impairment may stem from abnormal stimulus integration. Such abnormal integration may disrupt the evaluation of threat within fronto-cortical regions.

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Introduction

A key aspect of social cognition and communication is perception and appraisal of facial affect. Understanding the neural basis of such perception has begun through integrating studies on emotion processing in patients with brain lesions,[1,2] and animal paradigms.[3,4] These efforts provided a basis for neuroimaging and electrophysiological investigations that have identified the major components of a neural network, apparently centered on the amygdala (AMY).[5] The neuro-modulatory role of affect on face processing has been most clearly elucidated in the perception of fear.

Facial affect appraisal can be conceptualized as a hierarchical and synergistic processing stream involving 3 stages: sensation, integration, and evaluation[48]. In this model, sensation of facial stimuli begins subcortically with visual input passing from the superior colliculi to visual thalamus, from where it proceeds primarily to visual (primary and association) cortex (OCC). The visual input is interpreted as threat related by the AMY, which correspondingly activates stimulus integration associated temporal regions (STG), memory regions—hippocampus and middle temporal gyrus—and ''executive'' regions in inferior frontal (IFC), medial frontal (MF), and prefrontal (PFC) systems. The evaluative phase may or may not produce a response, presumably mediated through the PFC. In addition to this pathway there is increasing evidence that crude visual input, sufficient for subliminal fear signaling, proceeds directly from THA to AMY bypassing visual cortex.[6]

Impaired facial affect recognition is a prominent feature of schizophrenia (SCZ)[7–10] that is linked to negative symptom severity and poor functional outcome.[9,11–13] These deficits are most prominent for the detection of threat-related emotions such as fear and anger and may underlie more general deficits in the perception of threat signals.[14] Facial affect neuroimaging studies to date have focused on abnormal amygdala activity and dysfunction in the perception of threat expressions.[15–21] These studies have employed differing methodologies, with most indicating reductions in amygdala activity[21–26]

during facial affect identification and others indicating increased right amygdala tonic activation.[19,27] While results may reflect differences in task demands, they could also point to differences between task-related activation, measured in blocked trials,[24] and those related to the appearance of specific stimulus classes and measured with event-related designs.[15] Thus, while overall activation during an emotion identification task could be lower, when contrasted with a baseline where there is no task to perform, there could still be increased activation for a specific stimulus class, such as the appearance of fearful faces, and this can be ascertained by event-related analyses. In addition to amygdala effects, these studies have shown activation differences within both sensory aspects of the facial affective processing stream, such as visual cortex, integration regions such as fusiform and medial and superior temporal gyrus, and executive inferior frontal regions. However, few studies[25,28] to date have examined the functional connectivity differences between groups among these regions of interest (ROIs).

The majority of these studies examined task-related activation, and patient's performance was either carefully examined (eg, as a variable) or tasks were constructed to minimize performance difference so as to avoid confounding of physiologic measures. In cases where performance was evaluated, it did not explain the difference in activation patterns. However, it is unclear whether activation differences seen in affective identification tasks are due to problems in the evaluation of facial affect or due to a core inability to integrate sensory input. For example, from a cognitive neuroscience perspective, if the task is to identify emotions, sensitivity of any node in the system to specific stimuli may disrupt subsequent processes required for the ultimate response.

We have recently examined this hypothesis[15] by comparing patients with schizophrenia to healthy controls both for task-related activation, when compared with a resting (cross-hair) baseline, and for event-related activation linked to the appearance of a specifically valenced face compared with the appearance of a neutral face. In this event-related contrast, the evaluative aspect of the task is held constant and activation therefore reflects stimulus-related effects. With this event-related analysis, we could also examine separately activation for correct and for error trials in emotional face evaluative tasks. We reported that for threat-related (fear and anger) stimuli, patients showed greater amygdala activation than controls overall. Furthermore, patients and controls showed similar activation for correctly identified stimuli, but very different effects led to errors in affect identification. Whereas in healthy subjects, greater limbic activation was higher for correct trials than incorrect trials, the inverse was observed in schizophrenia. Thus, patients' amygdala activity was higher during error trials compared with correct trials. This exaggerated activation for fear expressions in the amygdala robustly correlated with negative symptoms. Notably, this pattern of abnormal activation to errors was observed across multiple nodes within the affect processing network including regions implicated in the sensation, integration, and evaluation.

These findings suggest that patients with schizophrenia have deficits related to modulation of the neural circuitry recruited for affective appraisal, which underlie the threat detection abnormalities in the illness. However, the stage of processing at which these deficits occur remains difficult to discern. Prior studies of facial perception, as well as basic visual perception, have suggested that patients have core deficits in visual processing ability including iconic memory,[25,29] spatial frequency and contrast sensitivity perception[30,31] and configural processing.[32–35] However, it is unclear how such core aspects of visual processing might contribute to impaired threat detection in faces. Here, we report an exploratory functional connectivity analysis conducted to better describe where, within the affective appraisal network, abnormal internodal connectivity might occur during threat detection. We expected a connectivity analysis to reveal between-group differences not apparent in the initial analysis that examined overall mean differences in activation between groups across performance. Specifically, we examined the intercorrelations among activation measures in brain regions comprising the facial affect processing nodes. These correlations would reflect the extent to which activation in one region is proportional to that in another. Differences in the correlation patterns between groups were tested using a recently developed method, CORANOVA, which allows for testing differences among "correlated correlations."[36] We used CORANOVA to identify regions where patients and controls differ in size of correlations, relative to other regions.

We hypothesized that a core dysfunction in the processing cascade involved in the appraisal of facial affect would be revealed by altered connectivity among regions involved in the cascade. For example, deficits in perception and integration of visual features might lead to maladaptive evaluation of threat related signals. This would be reflected in differing correlation patterns between groups within occipital and temporo-limbic circuits and altered connectivity between these nodes and frontal evaluative brain regions.

Method

This analysis is based on a previously published study.[15] Therefore, image acquisition parameters and image analysis details are only summarized here.

Subjects

The original sample included 16 patients with schizophrenia (12 men) who met DSM-IV, criteria for schizophrenia or schizoaffective disorder and 17 healthy controls (12 men). The patients were somewhat older

on average (30.1 ± 6.5 SD, years; controls 25.0 ± 3.9, t = 2.73, df = 31, $P < .01$) and, as expected, had lower education (12.8 ± 2.3, range 9–16 years; controls 15.8 ± 2.2, range 12–20, t = 3.72, df = 30, $P < .01$). However, they had comparable averaged parental education (patients 14.1 ± 3.6, range 7–20; controls 16.3 ± 2.9, range 9–20, t = 1.95, $P < .06$). After complete description of the study, written informed consent was obtained.

The schizophrenia sample included stable outpatient with mild symptoms at time of study. Global ratings on the Scale for Assessment of Negative Symptoms (SANS)[37] averaged 1.3 ± 0.9 (range 0–3.0) and ratings on the Scale for the Assessment of Positive Symptoms (SAPS)[38] averaged 1.4 ± 0.6 (range 0–2.3). Age of onset of psychotic symptoms in the context of functional decline was 20.1 ± 3.8 (range 12–29), with illness duration of 9.6 ± 7.1 years, and 3.6 ± 4.1 (range 0–15) psychiatric hospitalizations. At the time of imaging, all patients, except one, were on stable doses of antipsychotics: 2 received first-generation (CPZequiv = 542 ± 292 per day),[39] 11 second-generation (OLZequiv = 18.2 ± 2.8 per day), and 2 both (CPZequiv = 16.7 per day, OLZequiv = 11.3 per day) medications.

Imaging Tasks

The face emotion identification task included 4 conditions (separate time series), presented in a counterbalanced order, each with a specific target expression: happy, sad, anger, or fear. Stimuli were selected from a set validated in healthy people and patients with schizophrenia.[40] Each condition included four 90 second (s) blocks of emotion identification, separated by 24 s of rest during which a scrambled face with a central cross-hair for fixation was displayed. Each block contained 8 target faces (eg, 8 fear), 12 foil faces (eg, 4 happy, 4 sad, 4 angry), and 10 neutral faces. Thus, a condition included a total of 120 faces: 32 targets, 48 foils, and 40 neutral in a pseudorandom sequence. Faces appeared for 3 s and participants endorsed "target" or "other" using the 2-button response pad. Within a block, target expressions (eg, fear) and foil expressions (eg, happy, sad, or anger) were separated by a variable number of neutral faces (range 0–5 faces = 0–15), allowing for event-related modeling of the hemodynamic response with neutral faces as a within-block baseline. This interblock design also permitted modeling of events based on accurate target identification and errors. Abbreviated response instructions remained visible throughout the task. The same faces were cycled through the 4 conditions serving as targets or foils depending on the condition. Each condition (time series) lasted 8 min with total task duration ~32 min.

Image Acquisition

Detailed image acquisition and processing methods were described previously.[15] Briefly, data were acquired on a 4-T GE Signa Scanner (Milwaukee, Wisconsin), employing a quadrature transmit and receive head coil. Structural images consisted of a sagittal T1-weighted localizer, followed by a T1-weighted acquisition of the entire brain in the axial plane (24-cm feild of view [FOV], 256 × 256 matrix, resulting in voxel size of .9375 × .9375 × 4 mm). This sequence was used for spatial normalization to a standard atlas[33] and for anatomic overlays of the functional data. Functional imaging was performed in the axial plane using a 16-slice, single-shot gradient-echo (GE) echo-planar (EPI) sequence (time to repetition [TR]/echo time = 1500/21 ms, FOV = 240 mm, matrix = 64 × 40, slice thickness/gap = 5/0 mm). This sequence delivered a nominal voxel resolution of 3.75 × 3.75 × 5 mm. The 5-mm slice thickness was a compromise to permit optimal visualization of the amygdala with minimal sacrifice in brain coverage. Total slices per volume were also limited by a 1.5-s TR, which was selected to provide 2 volume acquisitions per stimulus exposure (3 s per face). The slices were acquired from the superior cerebellum up through the frontal lobe. Inferiorly this corresponded to a level just below the inferior aspect of the temporal lobes and superiorly to approximately the level of the hand-motor area in the primary motor cortex.

Connectivity Analysis

This analysis was conducted solely for the fear condition and for its target stimuli (=32). As reported previously,[15] there was no significant behavioral performance difference between groups. We focused on fear detection as overall limbic activation was reduced in patients compared with healthy subjects. Further analysis that examined correct and incorrect responses in each group separately had shown that while in controls error trials were associated with reduced activation within multiple nodes of the facial affective network, the opposite pattern was observed in schizophrenia patients. These combined findings suggested that the pattern of overall communication between nodes within the affective neural network, regardless of performance, might be abnormal in patients. Hence, we examined performance, across both correct and error trials.

All connectivity analysis was conducted on ROI estimates of blood oxygen level–dependent (BOLD) signal change, observed in contrasts of fear vs neutral faces. Whole brain analysis employed a voxel-wise significance criterion of a minimum Z threshold of 2.3 and a cluster significance of $P < .05$. For each ROI, "Energy" was calculated as average BOLD percent signal change multiplied by the number of activated voxels.

CORANOVA

Given the intuitive appeal of correlations, we examined connectivity by using the correlation coefficients among the activation indices obtained from the ROIs in which Energy was greater for fearful than neutral faces. To

Table 1. ROIs In Which Activation (Energy Levels) Fear Faces > Neutral Faces

ROI (Abbreviation)	Talairach $-x$-y-z Coordinate Space[a]
Occipital lingual gyrus (OCC)	14, 78, 10
Posterior cingulate gyrus (CGP)	−4, 46, 20
Brainstem (BS)	−6, 28, 26
Visual thalamus (THA)	10, 20, 6
Amygdala (AMY)	22, −4, 20
Caudate nucleus (CN)	10, 8, 6
Middle frontal gyrus (MF)	32, 28, 32
Inferior frontal gyrus (IF)	42, 22, 2
Prefrontal cortex (PFC)	−8, 40, 26

[a]Values represent coordinates for left hemisphere right hemisphere ROIs were symmetrically placed.

properly examine the pattern of these correlations, as well as correlation differences between groups, standard homogeneity tests of correlations such as the Fisher's Z test are inappropriate. For within-sample contrasts, activation in each ROI is itself correlated with other regions, and thus correlations among amygdala, IF, and STG are "correlated correlations."[41] Further, standard testing approaches for the comparison of correlations are based on assumptions of asymptotic normality and require large sample sizes.[36] Here, we wished to compare the correlations between schizophrenia patients and healthy controls across brain regions and examine the "interaction" between brain region and group in determining the size of correlations. CORANOVA[36] is a nonparametric approach for testing the homogeneity of correlations for such main effects and interactions.

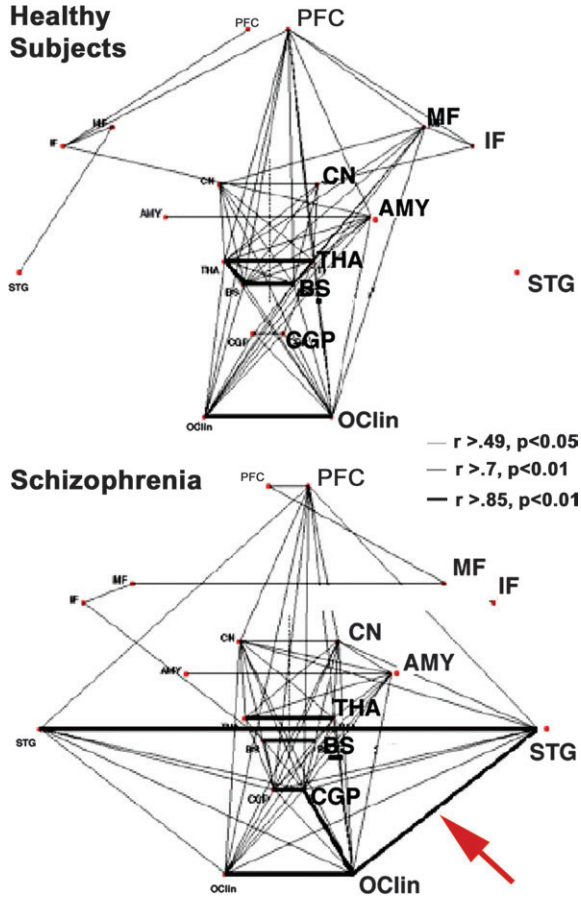

Fig. 1. Anatomically Represented Correlations Among Fear-Activated Brain Regions. Talairach x-y coordinate correlations among the 9 regions activated by fearful faces in controls (top row) and patients (bottom row). Red arrow indicates a CORANOVA significant correlation difference.

Results

CORANOVA Correlation Analysis

We examined connectivity by using the correlation coefficients among the ENERGY indices obtained from the different regions across correct and error trials. ROIs in which ENERGY during fear faces presentation was significantly greater than neutral face presentations included the 10 regions are listed in table 1.

Intercorrelations of the energy measures varied considerably among regions, with some reaching very high magnitudes (>0.9) and others nil. To better visualize the pattern of these correlations, we employed a graphic program written as a SAS macro[42] that presents the ROIs in their Talairach x-y-z coordinate space and correlations as connecting lines, with thickness reflecting magnitude (all lines representing correlations with a $P < .05$). This "connectograph" was applied to the 10 regions identified as showing time-locked changes to fear faces compared with neutral faces (table 1). As seen in figure 1, while controls showed connectivity mostly in medial structures and between medial and frontal structures, in patients there was extensive connectivity with STG for almost all regions including frontal cortex and AMY. At the same time within schizophrenia patients, there were fewer and weaker medial to frontal correlations, and there were no significant IF or MF to PFC correlations.

Significance testing using CORANOVA (300 bootstraps, 1000 permutations) of these correlation patterns by group showed that patients had a higher correlation between right STG and right occipital lingual gyrus than in healthy controls ($P < .02$).

Discussion

Patients with schizophrenia consistently show deficits in the ability to perceive facial affect. Such deficits are linked to social cognitive dysfunction and to poor global outcome.[43] These deficits are most profound for the perception of threat-related emotions such as fear and anger. It is unclear whether these deficits reflect dysfunction in sensory integration neural regions, impairment in

downstream evaluative systems, or the connectivity between them.

In the present study, we examined connectivity by evaluating the pattern and strength of intercorrelations among task-activated brain regions in both schizophrenia and healthy subjects regardless of performance. We found that schizophrenia patients displayed connectivity between STG and OCC, THA AMY and PFC, which was not significantly present in healthy controls. The CORANOVA indicated that correlations between STG and OCC were differentially higher in patients than controls. Further, unlike healthy subjects, schizophrenia patients did not show significant connectivity between medial structures such as AMY and THA, and frontal evaluation (MF, IF), and response (PFC) brain regions. Thus, it appears that in patients the increased connectivity between visual and integrative nodes of the facial affect evaluative system is associated with reduced connectivity among other components.

Our CORANOVA analysis suggests dysfunction in what Haxby[44] has termed ''core systems'' of visual processing. Indeed, schizophrenia patients display a wide variety of basic visual processing deficits, including impaired contrast and spatial perception,[30] as well as configural and feature processing deficits,[32–35] which may be linked to facial affect perception deficits. Such a hypothesis has been suggested by Taylor,[27] who points to hyperactive and less-focused parieto-occipital responses to basic visual stimuli. Taylor[27] suggests that emotional perceptive dysfunction in schizophrenia may stem from poor coordination between neural nodes of emoto-cognitive circuits. In neural network models of facial affect processing derived from facial configural feature classification algorithms, Johnston et al[45] demonstrated that by inserting random noise or ''lesioning'' connections within the model yielded deficits in the detection of fear, anger, and disgust. This deficit profile is similar to that seen in schizophrenia and suggests that dysfunction in patients may reflect more generalized processing dysfunction rather than a specific emotional deficit. Conceivably, the abnormal OCC-STG connectivity in patients, suggested by our CORANOVA, might indicate inefficient feature integration of facial expressions. This maladaptive integration may reflect greater overall noise or disruptions within the affective appraisal network including core visual systems, as Johnston et al's[45] network model predicts. Thus, perhaps basic visual-temporal dysfunction leads patients to ''overprocess'' core visual and configural information, resulting in maladaptive appraisal of threat within frontal circuitry.

Our finding of significant THA-AMY-prefrontal connectivity in controls but not patients is consistent with the connectivity findings of Fakra et al.,[28] which suggest that patients may employ a cognitive feature–based analysis for facial affect in order to compensate for limbic dysfunction. Alternatively, prior connectivity analysis[25] has also suggested that prefrontal monitoring system dysfunction in schizophrenia may stem from disconnections within a subcortical fear detection pathway. The current study is unable to resolve this issue.

This study was exploratory in nature and utilizes a novel approach for assessing connectivity. A potential limitation of this study is that the analysis is based on an image acquisition scheme that focused on the amygdala and does not encompass the whole brain. Future connectivity studies with whole brain acquisition could examine orbito-frontal and executive brain systems not included in our models. This study focuses on fear detection, as it was promted by aberrant limbic activation to the appearance of fearful faces and a paradoxical activation pattern in patients during error trials. Future studies will examine the patterns of connectivity during the processing of other emotions.

Importantly, the presence of these correlation patterns cannot be used to imply causality. Future studies with larger samples and hence more power should employ Structural Equation Modeling,[46,47] which has the ability to examine both direct and indirect (mediating) effects between neural nodes of the affective appraisal network. More generally, the affective appraisal network is undoubtedly much more complex than aspects characterized here. Future study could take these complexities into account.

In view of these limitations, the present study should be considered more illustrative than definitive. It was aimed to show that in addition to the current emphasis on examining regional activation, information could be gleaned from exploring the intercorrelations among activations in nodes of a network. Such correlations may reveal specific differences in their magnitude, which could help identify regions that show abnormal connectivity that can interfere with information processing.

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