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Functional disconnection between the visual cortex and right fusiform face area in schizophrenia

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ABSTRACT

Patients with schizophrenia show impairment in processing faces, including facial affect and face detection, but the underlying mechanisms are unknown. We used functional magnetic resonance imaging (fMRI) to characterize resting state functional connectivity between an independent component analysis (ICA)-defined early visual cortical network (corresponding to regions in V1, V2, V3) and *a priori* defined face-processing regions (fusiform face area [FFA], occipital face area [OFA], superior temporal sulcus [STS] and amygdala) using dual regression in 20 schizophrenia patients and 26 healthy controls. We also investigated the association between resting functional connectivity and neural responses (fMRI) elicited by a face detection paradigm in a partially overlapping sample (Maher et al., 2016) that used stimuli equated for lower-level perceptual abilities. Group differences in functional connectivity were found in right FFA only; controls showed significantly stronger functional connectivity to an early visual cortical network. Functional connectivity in right FFA was associated with (a) neural responses during face detection in controls only, and (b) perceptual detection thresholds for faces in patients only. The finding of impaired functional connectivity for right FFA (but not other queried domain-specific regions) converges with findings investigating face detection in an overlapping sample in which dysfunction was found exclusively for right FFA in schizophrenia during face detection.

1. Introduction

Patients with schizophrenia exhibit face perception impairments, including difficulty perceiving emotional expressions, (Kohler et al., 2009; Norton et al., 2009) detecting faces, (Chen et al., 2009) and identifying individual faces (Ekstrom et al., 2016). The mechanisms underlying these perceptual problems, however, are unknown. Face perception is supported by a brain network that includes both domain-general (visual perception processes not specific to faces such as edge detection or perceptual grouping) and domain-specific (visual processing that is specific to faces) visual processing regions. The core domain-specific components of this network include fusiform face area (FFA), (Kanwisher et al., 1997) occipital face area (OFA), (Gauthier et al., 2000) and superior temporal sulcus (STS) (Puce et al., 1998). The amygdala, while not domain- specific for faces, is also considered part of this core network in that it is implicated in the processing of facial emotion (Haxby et al., 2000; Vuilleumier and Pourtois, 2007). These structures form a distributed network (Haxby et al., 2000) in which recurrent connectivity among domain-general early visual areas like V1 and V3 (Kim et al., 2006) and domain-specific brain regions like OFA and FFA, are critical for face perception (Rossion et al., 2003).

Neither the relative roles of domain-general versus domain-specific brain regions, nor the functional connectivity between the two, are well understood in relation to face perception impairment in schizophrenia. Previous studies have yielded inconsistent results regarding the nature of the dysfunction for face processing in schizophrenia. Some studies have implicated dysfunction in domain-general processes, such as preserved FFA responses in passively viewing faces (Butler et al., 2008; Yoon et al., 2006), while others have implicated domain-specific brain areas or processes, such as dysfunctional FFA or face-specific electrophysiological responses (Ekstrom et al., 2016; Herrmann et al., 2004; Maher et al., 2016b; Maher et al., 2016a). None of these studies focused on connectivity between brain regions.

One method for investigating the connectivity of brain networks and regions is the resting state network (RSN) approach. When employed with functional magnetic resonance imaging (fMRI), this approach quantifies spontaneously occurring temporal correlations in blood oxygenation level dependent (BOLD) fMRI signals across the brain when participants are instructed to rest and "do nothing" - that is, when they are not given a specific task to perform. Different statistical approaches can be used to tease apart BOLD signals emanating from different brain networks active during resting-state; these brain networks

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map onto the same networks required to perform tasks (Smith et al., 2009). Intrinsic fluctuations in BOLD signal have been shown to reflect electrophysiological activity of the brain at rest (Brookes et al., 2011) and functional connectivity is closely tied to anatomic connectivity (Snyder and Raichle, 2012). Thus, assessing the resting state functional connectivity of brain networks can provide information about the general properties of brain networks that may underpin activation during task performance. Considering the lack of agreement in previous studies regarding the neural dysfunction underlying problems with face perception in schizophrenia, investigating the functional connectivity of the core domain-specific and domain-general brain structures might yield insight into the nature of this deficit.

Few studies have reported dysregulated connectivity of brain regions that support visual perception or face perception in schizophrenia. Two reviews (Karbasforoushan and Woodward, 2012; Mwansisya et al., 2017) summarized findings on RSNs in schizophrenia patients and healthy individuals and found no evidence of group differences in brain areas subserving visual perception. Rather, findings consistently showed differences between both first-episode and chronic schizophrenia patients and controls in medial or dorsolateral prefrontal cortex, posterior cingulate cortex, and anterior cingulate cortex.

Among studies that have reported RSN differences between schizophrenia patients and controls in brain regions thought to be involved in visual perception, the specific regions implicated varied across studies. Further, most of those studies were not investigating *a priori* activation-based loci associated with face perception, for example, finding a difference in fusiform gyrus rather than in the fusiform face area localized within fusiform gyrus (Argyelan et al., 2014; Guo et al., 2014). A meta-analysis by Kühn and Gallinat (2011) found some agreement across studies for hyperactivation in bilateral lingual gyrus in schizophrenia subjects relative to controls. Argyelan et al. (2014) also found that lingual gyrus and bilateral occipital fusiform gyrus were two of six areas (out of 266 *a priori* defined regions) that showed weaker connectivity across brain areas in schizophrenia and bipolar disorder patients compared with controls, and that deficient connectivity in these structures was associated with worse neuropsychological performance on the Hopkins Verbal Learning Test (HVLT), working memory (Wechsler Memory Scale III), and speed of processing (Trail Taking Test A). Arbabshirani et al. (2013) showed that connectivity between a medial visual RSN and a temporal network was one of the most predictive of patients' clinical status when RSNs were used as a classifier. In comparing two different techniques for assessing functional connectivity, independent component analysis (ICA) versus seed based correlation analysis, Mannell et al. (2010) found group differences in occipital and temporal networks that included BA 18, but only for the ICA approach. Meda et al. (2012) compared connections between ICA-defined RSNs in patients and healthy individuals, and found differences in connectivity between a putative visual network and meso-paralimbic networks. Perhaps most relevant to the current study, Guo et al. (2014) found less functional connectivity in resting state functional homotopy, or connectivity of analogous regions between hemispheres, for fusiform gyrus in patients compared with controls. Overall, there is sparse research investigating connectivity differences in structures implicated in face processing, or examining the association between connectivity and perceptual performance during face processing in relation to schizophrenia.

The primary aim of this study was to use resting-state fMRI to examine functional connectivity between the early visual cortex and other face-processing regions (FFA, OFA, STS and amygdala) in schizophrenia patients and healthy controls.

A secondary aim was to evaluate how the functional connectivity of these face-processing regions may be related to (1) performance on a face detection task, and (2) brain activation during the same face detection task. To address this secondary aim, we used perceptual performance and fMRI data from a previous study (Maher et al., 2016b) whose samples partially overlapped with the current sample.

2. Materials and methods

2.1. Participants

Twenty-seven patients with schizophrenia and twenty-eight healthy controls participated in this study. For all subjects, inclusion criteria were 1) age between 18 and 60 years, 2) no history of diagnosed neurological diseases (e.g., seizure), and 3) no substance abuse or dependence within the preceding six months.

For patients, diagnoses were made based on a structured clinical interview (DSM IV, [First et al., 1994]) conducted by experienced clinicians, and by a review of all available medical records. All patients were taking antipsychotic medications (mean chlorpromazine [CPZ] dose equivalent was 349.6 mg; SD = 432 mg [Woods, 2003]) Symptom severity levels were assessed using the positive and negative syndrome scale (PANSS, [Kay et al., 1987])

Healthy controls did not meet criteria for an Axis I psychiatric disorder according to a standardized interview based on the SCID-I/NP (First et al., 1994) All healthy controls confirmed, via self-report, no knowledge of Axis I psychotic disorders among their first-degree relatives.

The two groups did not differ in age ($p = 0.68$), gender, or estimated verbal IQ (WAIS-IV; $p = 0.1$). Demographic information is provided in Table 1. All participants had normal or corrected-to-normal visual acuity, as assessed by the Rosenbaum Pocket Vision Screener. Handedness was assessed using the Edinburgh Handedness Questionnaire (Oldfield, 1971) All participants were right-handed except for one patient and one control.

Among the subjects who participated in this resting state study, thirteen patients and eighteen controls had also participated in a different study that examined neural activation in a face detection task (Maher et al., 2016b), which was performed during the same scanning session before the resting state scan. We used the imaging and perceptual performance data from that previous study in that subset of subjects, along with resting state functional connectivity data from the current study, to address the relationship between resting and task-driven neural responses.

2.2. Procedures

2.2.1. Image acquisition

MRI data were collected at the McLean Hospital Brain Imaging Center (Belmont, MA) on a 3.0 Tesla Siemens TIM Trio scanner (Siemens AG, Erlangen, Germany), using a 32-channel head coil. High-resolution structural images (TR = 2.1 s, TE = 3.3 ms, slices = 128, matrix = 256 × 256, flip angle = 7°, resolution = 1.0 mm × 1.0 mm × 1.33 mm) were used to register subjects' imaging data to a standard space and were also reviewed by a neuroradiologist to rule out neuroanatomical abnormalities. FMRI data for the 6 min run were collected for 32 3.5 mm axial slices covering the whole brain, with TR/TE = 2000 ms/30 ms, flip angle = 30°, matrix = 64 × 64 on a 220 mm × 220 mm FOV, in plane resolution = 3.44 mm × 3.44 mm, multiband factor = 8 (Feinberg et al., 2010; Tong and Frederick, 2014).

2.2.2. Image preprocessing

Preprocessing and statistical analysis of resting state data were done using FMRI Expert Analysis Tool (FEAT) version 5.0.6 (FMRIB's Software Library, http://www.FMRIb.ox.ac.uk/fsl). Preprocessing of resting state FMRI data consisted of motion correction using MCFLIRT (Jenkinson et al., 2002) slice-timing correction (regular up), removal of non-brain material from images using BET (Smith, 2002) grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, spatial smoothing with a Gaussian kernel (full-width-at-half-maximum 5.0 mm), and high-pass temporal filtering (high-pass filter cutoff: 150 s [Niazy et al., 2011]). Registration of fMRI outcomes to MNI standard space (prior to group-level statistical analysis) was achieved by applying two transformations (in a single step) in which

Table 1
Participant demographics.

Group	N	Age (yrs)†	Estimated verbal IQ†	PANSS+	PANSS-	PANSSgen	Duration of illness (yrs)
Controls (all)	26 (f = 11)	42.38 (15.5)	113.5 (15.5)				
Patients (all)	20 (f = 7)	40.65 (12.4)	105.75 (15.5)	17.06 (4.5)	13.65 (4.1)	31.47 (6.9)	17.8 (12.5)
Controls*	18 (f = 9)	40.72 (15.6)	113.87 (16)				
Patients*	13 (f = 5)	46.31 (11.7)	106.23 (14.3)	17.5 (4.5)	14.42 (3.9)	31.92 (7.4)	17.9 (12.5)

Standard deviation in parentheses; †, no significant group difference; f, females; PANSS, positive and negative syndrome scale; PANSS+, PANSS positive scale; PANSS-, PANSS negative scale; PANSSgen, PANSS general psychopathology scale; *, portion of sample participating in the current RSN study and previous fMRI study.

each subject's fMRI images were registered to their structural images using FLIRT (Jenkinson et al., 2002) and each subject's structural image was registered to the MNI standard space using FLIRT with further refinement using FNIRT (Smith et al., 2004).

2.2.3. Study procedures

Participants were told to remain still with their eyes closed (van den Heuvel and Hulshoff Pol, 2010) A cutoff for excess motion of no >0.4 mm for absolute displacement, along with visual inspection of the raw fMRI data (viewing each subject's images in succession as movie intensity bands, excessive translations/rotations) was used to exclude subjects for excess motion.

Eight (2 HC, 6 SZ) subjects were excluded from analyses due to excess motion. Along with one other control subject removed for anomalous anatomy upon radiologist review (excessively large ventricles), this resulted in an analysis dataset comprised by 26 controls and 20 patients. In this dataset, no significant group differences were found for absolute displacement (mean displacement: HC = 0.147 mm vs. SZ = 0.157 mm; $p = 0.69$), indicating that the groups were matched for movement.

2.2.4. Image analyses

Functional connectivity was assessed using group ICA (GICA; [Beckmann and Smith, 2004]) to identify RSNs and dual regression (Filippini et al., 2009; Nickerson et al., 2017) to identify the RSN functional connectivity maps for each subject. GICA is a multivariate data-driven method for identifying RSNs from resting state fMRI data. GICA was used to identify a set of independent components, which are spatial maps corresponding to RSNs (signals of interest) and to noise (e.g., physiological noise and artifacts), that were common to the entire sample (all patients and controls). GICA dimensionality equaled to 30, which resulted in maps that reflected the large-scale RSNs similar to those found in other work (Beckmann et al., 2009) identified via visual inspection. Because GICA identifies components that are common to all subjects, dual regression was used to identify the RSN functional connectivity maps for each subject, i.e., the specific configuration of the network in each subject that reflects between-subject variability. The dual regression was performed in two steps. First, the subject's time-courses for each GICA component were extracted by regressing the GICA spatial maps against each subject's fMRI time-series via multivariate spatial regression. Then, the subject's network time-courses were used in a second multivariate regression against that subject's fMRI data to estimate a set of spatial maps of regression coefficients, with each spatial map representing that subject's functional connectivity map for the corresponding GICA map. These maps can be queried by ROI to yield connectivity values between each ROI and the corresponding RSN, where positive and negative values indicate that the ROI time-courses are positively or negatively correlated with the network time-courses (i.e., positive being in phase and negative being out of phase).

In this study, our hypotheses pertained only to the functional connectivity between brain regions associated with basic/early processing of visual stimuli and putatively domain-specific face processing. Accordingly, we restricted our analyses to visual RSNs, and four *a priori* ROIs implicated in face processing (OFA, FFA, STS, amygdala). MNI standard space coordinates for ROIs were based on previous studies of face-selective processing (Harris et al., 2012). They were as follows: left FFA (x = −40, y = −59, z = −23); right FFA (x = 42, y = −51, z = −24); left OFA (x = −41, y = −84, z = −17); right OFA (x = 44, y = −78, z = −17); left STS (x = −55, y = −50, z = 3); right STS (x = 55, y = −50, z = 3); left amygdala (x = −24, y = −5, z = −22); right amygdala (x = −24, y = 5, z = −22). ROIs were constructed by placing a 10 mm sphere around these coordinates.

The visual RSN we selected is comprised primarily of medial visual cortex and has been described in many studies (Beckmann et al., 2005; Damoiseaux et al., 2006; Licata et al., 2013; Smith et al., 2009). We refer to this network as the 'visual RSN' hereafter.

2.2.5. Statistical analyses

To test for differences in functional connectivity between patients and controls and across ROIs, an omnibus mixed ANOVA was performed with regression coefficients extracted from each ROI reflecting its functional connectivity with the visual RSN. The ANOVA had between-subjects factors of group (patient vs. control) and within-subjects factor of ROI (FFA, OFA, STS, and amygdala) and hemisphere (left vs. right).

To address our secondary aim, we performed correlations (Pearson's *r*) to describe the association between functional connectivity values and (a) perceptual threshold from an off-line psychophysical face detection paradigm that varied contrast to determine low-level perceptual detection thresholds (80% accuracy) for faces vs. non-face objects (images of trees) and (b) brain activation (fMRI) elicited by the same face detection paradigm using each subject's perceptual threshold. Correlations with functional connectivity values were performed for brain activations in response to stimuli presented at (1) the contrast level at which subjects reached threshold, (2) twice the threshold contrast level and (3) 100% contrast (the same across all subjects), where values for brain activations were for non-face objects (trees) subtracted from faces. Correlations were performed for only those ROIs that showed significant group differences in functional connectivity (note that identical face processing ROIs were used in the current RSN experiment and previous task fMRI experiment). For more detail see supplementary materials, or for a full description, see Maher et al. (2016b). Thus, three correlation analyses were performed for each ROI where significant group differences in functional connectivity were found. Since these correlations were of interest only to facilitate interpretation of group connectivity differences, a correction for multiple tests was not performed.

To establish or rule out general connectivity differences within the medial visual network, we conducted a whole brain exploratory analysis of the medial visual network connectivity maps using non-parametric permutation testing (FSL Randomise with cluster mass-based thresholding, 5000 permutations) to control family-wise error at $p < 0.05$.

3. Results

3.1. RSN of interest

The medial visual RSN extracted from the GICA, shown in Fig. 1, comprised brain areas in the occipital lobe, posterior to the parieto-occipital fissure and includes the cuneus, portions of the occipital pole corresponding to V1, V2, V3, and portions of Brodmann areas 17, 18, and 19. This medial visual RSN replicates that found previously

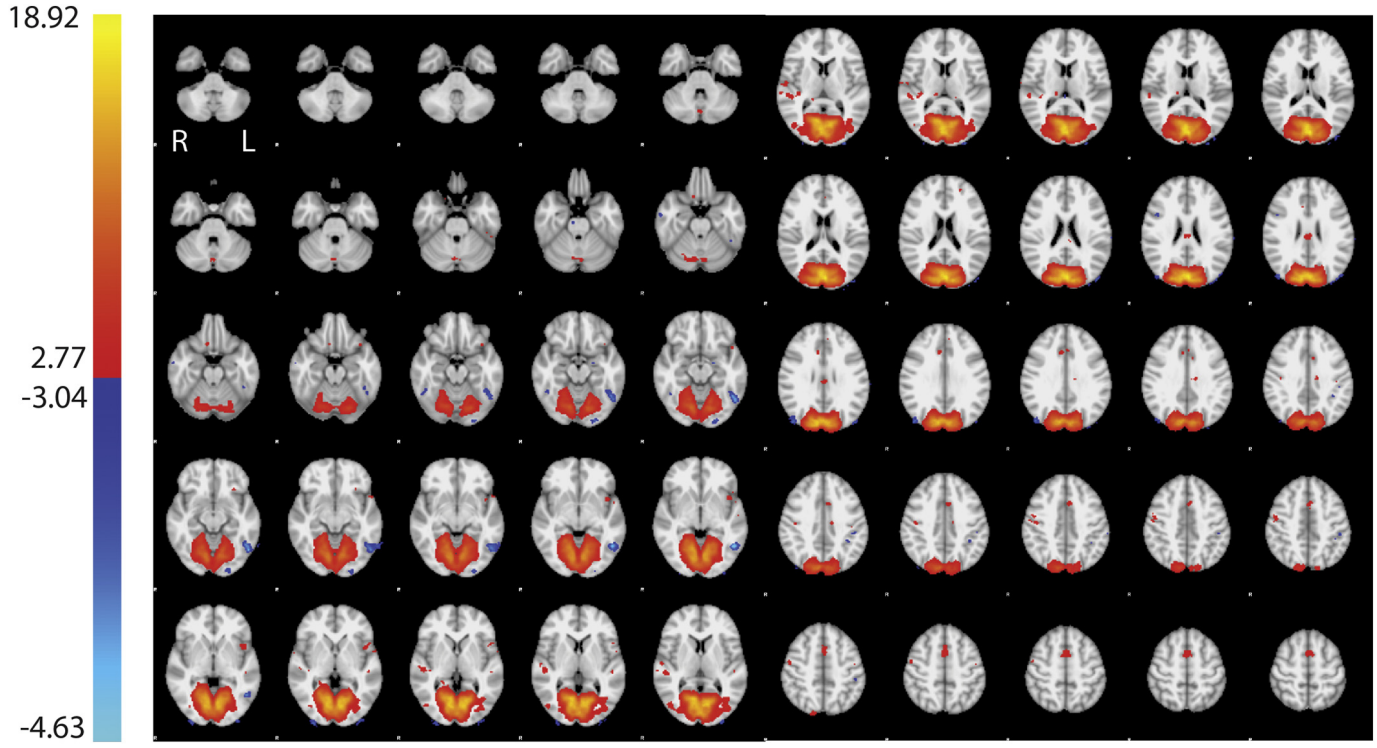

Fig. 1. Visual RSN. The medial visual RSN extracted using GICA (*Z*-values, with positive indicated by red-yellow and negative by blue-light blue) includes portions of functionally defined regions V1-V3 and Brodmann areas 17, 18, and 19.

(e.g., Beckmann et al., 2005, Fig. 6). As coordinates of this network are publically available, we compared the medial visual network found in our sample to Beckmann et al. (2005) and found a spatial cross correlation of 0.82 using the FSLCC function in the FSL.

There were no significant group differences in functional connectivity within the network at $p < 0.05$ FWE corrected.

3.2. Functional connectivity between face selective ROIs and the Visual RSN

Functional connectivity values (regression coefficients from dual regression) for each ROI with the visual RSN and a schematic showing group differences in connectivity strength (line thickness corresponds to absolute difference between schizophrenia and healthy controls, location approximate) are presented in Fig. 2A and B, respectively.

The omnibus ANOVA testing hypotheses regarding functional connectivity showed no significant ($p < 0.05$) group interactions or group differences, though the interaction of ROI x Hemisphere x Group was close to significant ($p = 0.051$). Given how close this result was to statistical significance, we followed up with tests at each ROI to characterize the differences driving this low probability (if not quite $\alpha = 0.05$) finding.

Four ANOVAs testing the functional connectivity of each ROI with the visual RSN yielded a significant group by hemisphere interaction for FFA ($F[1,44] = 6.56$, $p = 0.014$) only; group by hemisphere interactions for all other ROIs were not significant ($Fs < 2.6$, $ps > 0.12$). Follow-up *t*-tests showed that the interaction reflected a statistically significant group difference at right FFA ($p = 0.01$) but not left FFA ($p = 0.99$). No main effects of group were found for the other ROIs ($Fs[1,44] < 1.96$, $ps > 0.168$). A main effect of hemisphere (for all subjects combined across group) was found for STS and OFA ($Fs[1,44] < 4.6$, $ps > 0.04$).

3.3. Correlations between right FFA (rFFA)-visual network functional connectivity and face detection/neural correlates

Our secondary aim was to characterize the relationship between functional connectivity and perceptual thresholds/neural responses from the previous work that had subjects in common (13 SZ, 18 HC). This previous study showed that patients had overall higher (i.e., worse) perceptual thresholds for both faces and non-face objects. Neuroimaging results showed that patients had a relative lack of face selectivity (difference between responses to face vs. non-face objects—in this case, images of trees) compared with controls, and these effects were found in right FFA only.

In controls, no significant correlations were found between rFFA-visual RSN connectivity and perceptual thresholds for faces ($r = -0.18$) or trees ($r = 0.31$). In patients, rFFA-visual RSN connectivity values were significantly correlated with perceptual thresholds for both faces ($r = 0.62$, $p = 0.02$) and trees ($r = 0.61$, $p = 0.03$), such that higher perceptual thresholds were associated with stronger positive (in-phase) connectivity between rFFA and the visual RSN (Fig. 3A & C).

In controls, significant positive correlations were found between rFFA-visual RSN connectivity values and face-selective task-induced activations at rFFA (Fig. 3B & D) when stimuli were at perceptual threshold for contrast ($r = 0.53$, $p = 0.02$) and when stimuli were at 100% contrast ($r = 0.56$, $p = 0.02$), but not when images were shown at twice the perceptual threshold, although the direction of the relationship was consistent ($r = 0.36$). Since rFFA-visual RSN connectivity values were, on average, negative (out of phase) in controls (Fig. 3D), this pattern shows that the stronger the negative correlation between rFFA resting state fMRI signals and the visual RSN signals, the less the task-induced activation. Patients did not show a significant correlation between rFFA-visual RSN connectivity values and face-selective task-induced activations at rFFA for any of the contrast levels (Fig. 3B). The values for all contrast levels were negative in direction (*r*s between −0.2 and −0.36).

3.4. Correlations between rFFA-visual network functional connectivity and clinical variables

Neither the correlation between medication dose (based on CPZ equivalent) and rFFA-RSN connectivity ($r = -0.02$) nor between

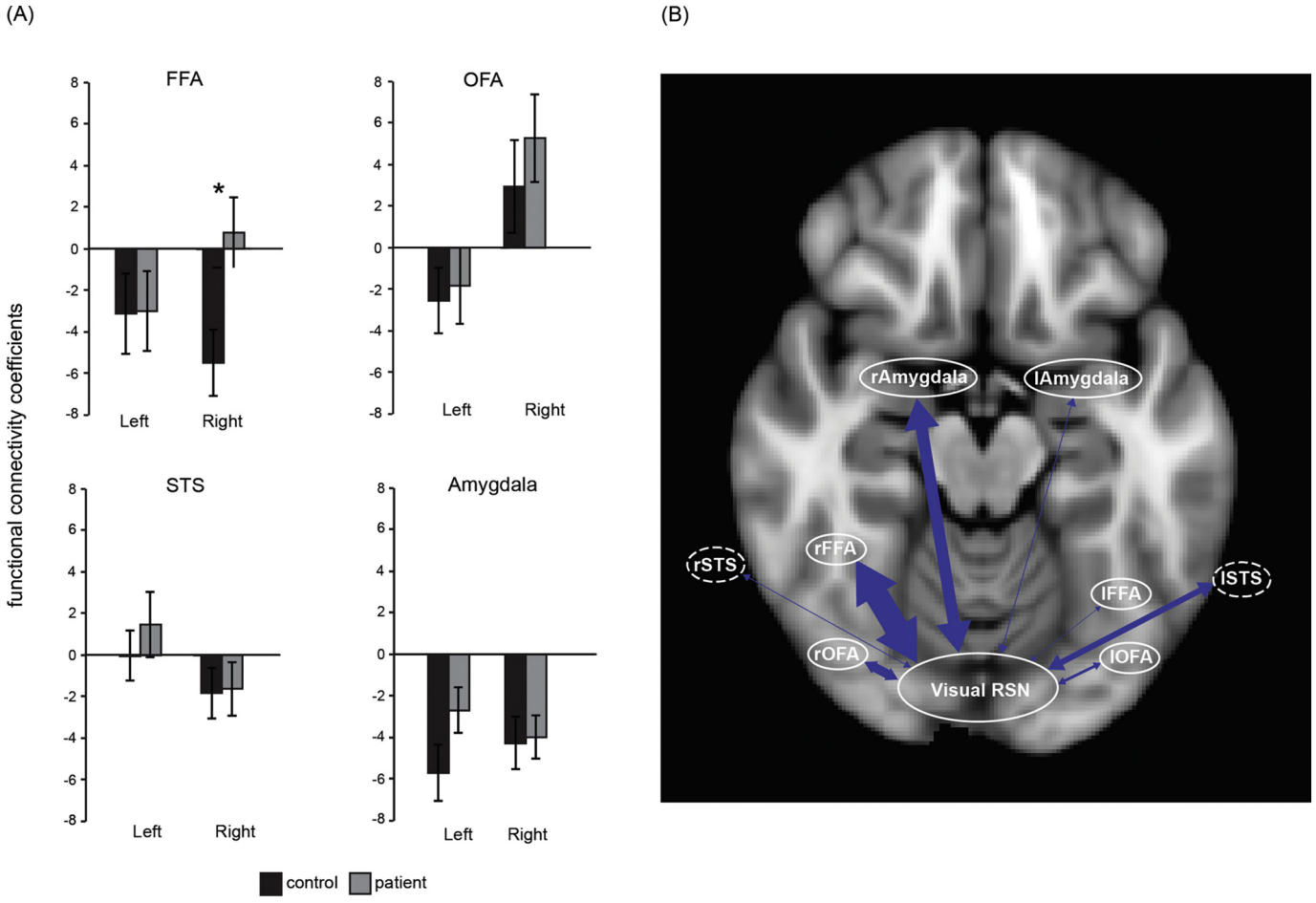

Fig. 2. Functional connectivity between each ROI and the visual RSN. Panel (a) bar graphs show connectivity values for each ROI with the visual RSN; controls are in black, patients in gray. Panel (b) shows a schematic (locations approximate) depicting the differences in magnitude of functional connectivity between patients and controls for each ROI with the visual RSN (line thickness reflects absolute value).

PANSS scores and rFFA-RSN connectivity (absolute value of *rs* ranged from −0.02 to 0.25) was statistically significant.

4. Discussion

We found that the strong negative resting state functional connectivity between the medial visual RSN and right FFA observed in controls was significantly reduced in schizophrenia. In contrast, functional connectivity between this network and other face processing areas (left FFA, OFA, STS and amygdala) was intact in patients. Our study fills a key gap in the literature by assessing the connectivity of face processing regions with the visual network comprising early visual areas. Many functional connectivity studies of schizophrenia focused on brain regions related to non-perceptual processes like executive functioning, with negative findings in visual areas being potentially dependent on the seed regions used for such analyses. In contrast, our method used a model free, data driven method for identifying RSNs (ICA) and queried brain regions defined *a priori* for sensitivity to faces, which may help explain the findings of impaired connectivity in visual areas.

The restriction of group effects to the right FFA is meaningful in light of literature showing that right FFA seems to have special functional significance, despite the fact that FFA is a bilateral cortical area (Kanwisher and Yovel, 2006). In healthy individuals the rFFA shows stronger activation to faces than left FFA (Kanwisher et al., 1997; McCarthy et al., 1997; Rossion et al., 2003; Rossion et al., 2000) and activation of rFFA to faces is more strongly associated with perceptual performance than is left FFA (Weibert and Andrews, 2015). Other work has shown that right FFA is more important than left in both acquired (Barton et al., 2002) and developmental prosopagnosia (Zhang et al., 2015). This pattern was also found in our fMRI results (Maher et al., 2016b) for face selectivity (face responses-tree responses), in that effects were larger on the right for all contrast levels, although this did not result in statistically significant interactions with hemisphere.

These results converge with other work (Quintana et al., 2003) showing that activation in right FFA is selectively compromised during face perception in schizophrenia patients. The activation-based perceptual detection task used in an earlier study from our group (Maher et al., 2016b) investigated the same face activation structures interrogated here in a partially overlapping sample, and showed a similar pattern: spared activations in all structures except for right FFA, a region that showed face selectivity (responses to face stimuli > than responses to non-face stimuli [trees]) in controls but not in patients.

We also conducted an electrophysiology study using the same face detection paradigm used in the fMRI study (along with some of the same participants) and found a deficit (lack of face selectivity for patients) on the N170 component (Maher et al., 2016a) that was present on the right but not the left. The N170, a right hemisphere lateralized negativity peaking around 170 ms after stimulus-onset, is a reliable marker of face detection that has been localized to the FFA, (Rossion et al., 2003; Watanabe et al., 1999). Accordingly, this electrophysiological deficit reflects convergent evidence for selective FFA impairment for face detection in schizophrenia in a sample partially overlapping with that of the fMRI study.

We also found that dysregulation in functional connectivity between the RSN visual network and this key face processing area was significantly associated with off-line face perception task performance and

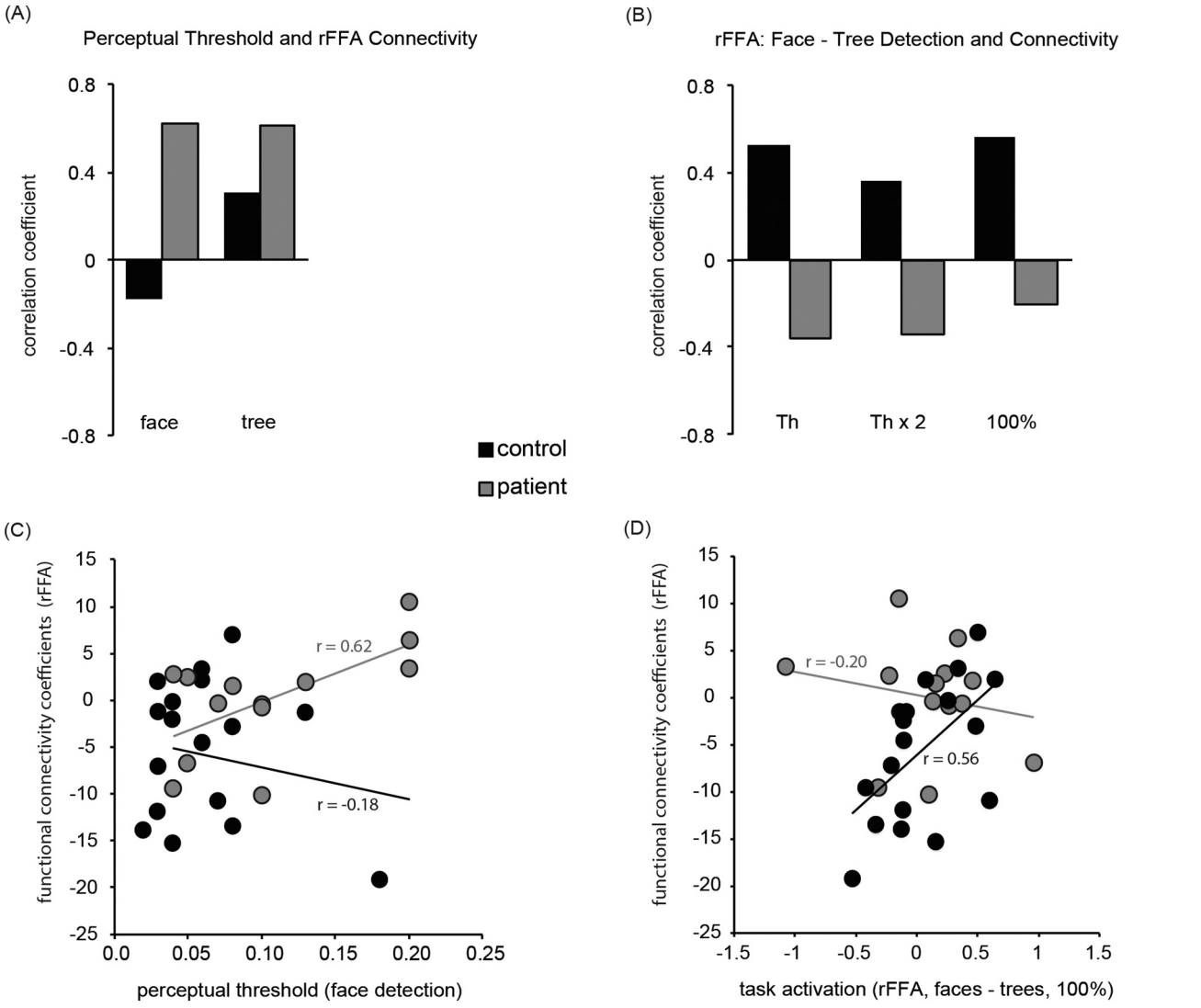

Fig. 3. Correlations with functional connectivity. Controls are in black, patients in gray. Panel (A) shows the correlation between rFFA-visual RSN connectivity values and perceptual thresholds for faces and trees. Panel (B) shows the correlation between rFFA-visual RSN connectivity values and face-selective (face – tree) rFFA task activation across contrast levels. Panels (C) shows a scatter plot of the relation between rFFA-visual RSN connectivity and perceptual threshold to faces and (D) shows a scatter plot of the relation between rFFA-visual RSN connectivity and face-selective (face – tree) rFFA task activation for the 100% contrast condition.

thus may be one mechanism underlying impaired face detection in patients with schizophrenia. This finding must be interpreted with caution, because it occurred in a small sample consisting of only 13 patients. Specifically, the greater the perceptual impairment in patients, the more positive (in phase) the connectivity between rFFA and the visual RSN (Fig. 3A & C). The direction of this relationship is not surprising considering that greater negative (out of phase) connectivity was found in controls than patients. This association did not differ by stimulus type, being moderately strong for both face and tree detection tasks. This finding is similar to task-induced BOLD results from our previous fMRI detection study showing that the rFFA responds similarly to faces and trees in patients. Controls showed no relationship between task performance and rFFA-visual RSN connectivity.

Controls, but not patients, showed a moderate relationship between functional connectivity and task driven fMRI responses. That is, greater negative connectivity between rFFA and the visual RSN predicted less task activation. While this may seem counterintuitive, previous work from our lab (Maher et al., 2016b) found that controls who performed best at face detection tended to show less activation (and activation in controls was less strongly associated with performance than it was in patients). We posited at the time that this might be due to greater efficiency in the rFFA in good performers, who need to recruit fewer resources to perform the same task. The same may be said of the association reported here: those who tend to activate less during the task have stronger negative functional connectivity between early visual areas and rFFA, allowing for greater efficiency.

Holistic processing of faces has been shown to be most important for face detection and recognition (Richler et al., 2011; Tanaka and Farah, 1993) The right hemisphere visual stream is thought to process more holistic form representations (Farah, 1991), and the FFA has been implicated in holistic representations of faces (Kanwisher and Yovel, 2006) rather than with particular facial features, which has usually been associated with the OFA (Guo et al., 2014; Liu et al., 2010). In both the perceptual task results and the connectivity results, only right FFA, and no other face-specific region (including OFA), showed dysfunction, suggesting that the difficulties patients have with face processing may involve the holistic level of face processing. This interpretation is consistent with other work that has shown evidence for global (as opposed to local) processing dysfunction for visual attention, (Granholm et al., 1999) early visual processing, (Johnson et al., 2005) and affective perception of faces (Fakra et al., 2008) in schizophrenia. Difficulties in processing faces at the holistic level may lead to greater reliance on

less efficient processes, such as a focus on particular facial features. This compensatory strategy would increase overall cognitive demands, requiring more cognitive resources to disambiguate input (Bar, 2003; Schendan and Maher, 2008), which in turn could exacerbate difficulties in social situations. Knowledge about the nature of face processing difficulties may help to inform perceptual training programs oriented around holistic processing of faces, which may in turn lead to improvements in social functioning.

4.1. Limitations

There is substantial overlap between the RSN connectivity sample presented here and the sample from the previous fMRI detection study used to investigate relations between functional connectivity and face detection performance/neural responses. Converging evidence from several modalities implicating the rFFA in face perception deficits is a strength, but independent replication is needed to ensure that the results are not sample specific. While *p*-values are reported with correlations, the primary purpose of this exploratory analysis was to describe the relationship between functional connectivity and performance/neural activation for face processing, so adjustments for multiple comparisons were not performed.

We assessed only regions for which we had an *a priori* hypothesis, and only in relation to one RSN. It may be that other functional connectivity deficits in the visual system that were not the target of investigation here are also present. Furthermore, functional connectivity based on correlations among fMRI signals cannot be interpreted to reflect direct connections between brain regions/networks, as correlations between fMRI signals can arise due to the modulation of both regions by a third region, or by artifact effects such as motion that can cause correlations between fMRI time-courses. This seems unlikely because participants with large amounts of motion artifact were removed from the resting state fMRI data. To more carefully examine the direct connections between brain areas/networks, causal connectivity methods are necessary. Future work will explore this approach.

The resting state scans came after the face detection task scans, leaving open the possibility that performing the task might influence the resting state scan. While we cannot preclude this possibility, the key comparison in this study is between the two groups, and the order of the scans was the same across groups.

5. Conclusion

This work documents selectively impaired functional connectivity between a medial visual cortical network and right FFA, but intact functional connectivity with other face activation regions (left FFA, OFA, STS, and amygdala) in schizophrenia. Combined with other work from our lab, these results show a convergence across modalities implicating selective dysfunction of right FFA that is not secondary to dysfunction at lower/earlier levels of visual processing. This conclusion is strengthened by (a) controlling for individual differences in face perception ability in face detection work, (b) the model-free technique we used to examine functional connectivity, (c) the correlations between perceptual deficits and imaging findings, and (d) the similarity of results across very different modalities: task-induced BOLD activations, electrophysiology, and functional connectivity. The convergence of these findings, revealing the same spared and dysfunctional brain regions using three different techniques, suggests that impaired face processing in schizophrenia may occur at the level of holistic face perception.

Contributors

SMM, LN, and YC designed the study. SMM and LN performed the data analysis. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

None of the authors have any conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.016.

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